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Original Communications

RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE IN THE NORTH AFRICAN AND MEDITERRANEAN THEATER OF OPERATIONS, UNITED STATES ARMY

LIEUTENANT COLONEL EDWARD F. BLAND
MEDICAL CORPS, ARMY OF THE UNITED STATES

INTRODUCTORY REMARKS

THE present study was undertaken on behalf of the Surgeon, Mediterranean Theater of Operations, United States Army, to determine the incidence of rheumatic fever and of rheumatic heart disease in Army personnel in this Theater, to observe the effect of wartime conditions upon their clinical course, to appraise the policies adopted for their management, and, finally, to scrutinize the measures now in force for the exclusion of susceptible individuals from overseas assignment. The material upon which this report is based consists essentially of both combat and service troops of the United States Army involved in this Theater from the original landings in North Africa in November, 1942, through the Tunisian, Sicilian, and Italian campaigns to the end of hostilities in May, 1945.

Two factors largely determined the method of approach adopted in assembling the data. First, in view of the now well-recognized chronic nature of rheumatic fever and the disabling effects of valvular heart disease developing therefrom, hospitalization and disposition of these patients overseas were essentially functions of the general hospitals. Second, approximately 95 per cent of the patients involved either were boarded for the Zone of the Interior (the United States) or for limited service, and copies of the board proceedings containing pertinent clinical data were retained by the hospitals and were available for review. Therefore, a study of the clinical records and of the board proceedings of the general hospitals is the basis for the greater part of the factual data recorded herein.

Received for publication March 23, 1946.

METHOD OF INVESTIGATION

During the two and one-half years covered by this report, seventeen general hospitals functioned in this Theater. At the time the final data were assembled, six of these hospitals had been transferred to France and information concerning their experience with rheumatic fever and rheumatic heart disease before leaving this Theater was obtained from the chief of the medical service of each by letter. In another instance (the 26th General Hospital), all records covering their sojourn in North Africa were destroyed by enemy action, but data on the Italian campaign were obtained from them through the chief of the medical service. The remaining ten general hospitals in operation in Italy were visited by me and their records were reviewed. In this fashion complete historical and clinical data were obtained on 841 individuals with rheumatic fever and/or rheumatic heart disease. This group of personally reviewed cases comprises the most valuable source of information in the study and serves as an index of the clinical features of the disease as it occurred in the United States Army in North Africa and Italy.

Next in importance is a smaller series of 100 patients included in the aforementioned group which I, in anticipation of a separate clinical report in collaboration with Captain Marlow B. Harrison, Medical Corps, studied at the 6th General Hospital. In this group we were especially interested in the antecedent history in regard to previous knowledge of heart disease from examinations at school, for insurance, for industrial employment, or for entrance into other branches of the service previous to their final acceptance by the Army, as well as their later experiences in medical establishments after entry into the service. This carefully questioned group, relative small though it is, serves as our principal check on the efficiency and thoroughness of induction examinations.

An additional source of data with reference to the incidence of asymptomatic and unsuspected rheumatic heart disease has been the records of the three medical laboratories to which protocols, as well as sections of tissue of all post-mortem examinations in this Theater, were sent for review and confirmation. Thus the records of the 2nd Medical Laboratory and of the 15th Medical General Laboratory have been studied, and from the 4th Medical Laboratory now in France pertinent data were received by letter. In this fashion 1,507 consecutive post-mortem examinations were available for our purpose.

To supplement this factual data, conferences were held with numerous individuals especially interested or experienced in this field at the headquarters of the Mediterranean Theater of Operations and of the 5th Army, and in the general, station, evacuation, and convalescent hospitals. As a result of these discussions there was agreement that rheumatic fever had been relatively infrequent, that rheumatic heart disease in the majority clearly antedated entry into the service, and, finally, that by limiting this survey to the general hospital, fully 95 per cent of patients with these conditions would be included. The remaining 5 per cent (estimated) would include the occasional patient who, contrary to the established policy in the Theater, was not referred to a general hos-

pital for appraisal, as well as a relatively small number of patients sent directly to the Zone of Interior by station or evacuation hospitals functioning temporarily in the role of a general hospital in newly occupied ports prior to the arrival of the latter. This was the case with the 8th Evacuation Hospital in Casablanca before the arrival of the 6th General Hospital, and, in like manner, of the 7th Station Hospital in Oran and the 52nd and 118th Station Hospitals in Naples. It is our belief, however, that the number of cases escaping attention in this fashion is negligible.

INCIDENCE

Clinical Data.—The over-all clinical data as to incidence assembled from the general hospitals for the two and one-half year period from November, 1942, to May, 1945, is summarized in Table I. In analyzing Table I, it should be remembered that in the process of evacuation a single patient may have been

TABLE I. INCIDENCE AND DISPOSITION OF RHEUMATIC FEVER AND/OR RHEUMATIC HEART DISEASE IN THE GENERAL HOSPITALS IN THE MEDITERRANEAN THEATER OF OPERATIONS, UNITED STATES ARMY (NOVEMBER, 1942, TO MAY, 1945)

GENERAL HOSPITALS	TOTAL CASES	DISPOSITIONS		
		ZONE OF INTERIOR	LIMITED SERVICE	DUTY
3rd*				
6th	183	169 (92.3%)	8 (4.3%)	6 (3.4%)
12th	178	135 (75.8%)	15 (8.5%)	28 (15.7%)
17th	96	91 (94.8%)	2 (2.1%)	3 (3.1%)
21st	85	72 (85.5%)	11 (13.0%)	2 (1.5%)
23rd*				
24th	40	28 (70.0%)	7 (17.5%)	5 (12.5%)
26th†	44	33 (75.0%)	0	11 (25.0%)
33rd	70	59 (84.3%)	7 (10.0%)	4 (5.7%)
36th	49	46 (93.8%)	0	3 (6.2%)
37th	34	23 (67.6%)	7 (20.6%)	4 (11.8%)
43rd	58	56 (96.5%)	2 (3.5%)	0
45th	134	134 (100.0%)	0	0
46th	58	56 (96.6%)	1 (1.7%)	1 (1.7%)
64th	30	29 (96.6%)	1 (3.4%)	0
70th	109	95 (87.1%)	8 (7.3%)	6 (5.6%)
300th	33	27 (81.8%)	4 (12.1%)	2 (6.1%)
Total	1,201	1,053 (87.6%)	73 (6.1%)	75 (6.3%)

*Information requested but not received at time of submission.
†Includes Italy only (see text).

hospitalized in more than one institution; hence, there is an estimated 10 per cent reduplication in these figures, which, however, it was possible to correct in the personally reviewed series of 841 cases which forms the basis of the clinical discussion later. The reduplication noted accounts in part for the disproportionately large number of cases from the 6th, 12th, and 45th General Hospitals, located, as they were, in or near ports of embarkation. An additional factor in connection with these three hospitals was their relatively early arrival and long

sojourn in the Theater. With due consideration for the various modifying factors in the available statistics, there were approximately 1,400 patients in the Mediterranean Theater of Operations with rheumatic fever and/or rheumatic heart disease.

Post-Mortem Data.—The post-mortem material available for study in this connection consists of protocols of 1,507 consecutive autopsies from the records of the 15th Medical General Laboratory and from the 2nd and the 4th Medical Laboratories. Reference has been made to these records in an attempt to arrive at some general idea of the incidence of presumably unsuspected rheumatic heart disease in the Army. As one might expect, the apparent incidence from these figures is low because they are weighted by the fact that most patients in whom valvular heart disease is discovered incidentally during hospitalization for other diseases or injuries are returned to the Zone of the Interior. However, in this series of 1,507 examined patients, there were fifteen instances of rheumatic heart disease in Army personnel, an incidence of 9.9 per 1,000. In thirteen of these fifteen, all of whom died of conditions unrelated to the heart, there were old well-healed lesions of mild degree, involving the aortic valve in two and the mitral valve in eleven. The remaining two patients had active rheumatic carditis. One of these is of considerable interest. This patient, 20 years of age, had pneumonia complicated by a lung abscess. During the course of the illness he developed acute migratory polyarthritis typical of rheumatic fever, a persistent tachycardia, and a loud apical systolic murmur which appeared while he was under observation. In the course of the illness he received five transfusions of whole blood. Following the last transfusion he developed icterus, anuria, and azotemia and died of renal failure. At post-mortem examination the heart weighed 350 grams. The endocardium of the mitral valve showed hemorrhagic areas and small linear verrucous vegetations along the line of closure typical of acute rheumatic endocarditis. Sections of the myocardium also revealed a widespread acute process with edema of the interstitial tissue, mild cloudy swelling of the muscle fibers, areas of hyperemia, and multiple small hemorrhagic foci. Sections of the mitral leaflet showed recent hemorrhagic infiltration together with diffuse infiltration by lymphocytes, plasma cells, and other mononuclear cells. No bacterial organisms were present in the vegetations. This case represents an initial acute attack of rheumatic fever complicating lung sepsis and a fatal transfusion reaction.

In connection with the post-mortem incidence of 0.9 per cent noted in this series, although the figures are not strictly comparable, it is interesting that Clawson reported an incidence of 2.8 per cent for rheumatic heart disease in 30,265 autopsies in Minnesota[1] and that Scott and Garvin in Cleveland found 1.7 per cent in 6,548 autopsies.[2]

Discussion.—Since rheumatic fever was included among the reportable diseases in this Theater, it is of some interest in the light of this survey to compare our findings with the number of cases formally reported to the Department of Preventable Diseases. It should be noted that our figures discussed in the

foregoing include both active rheumatic fever and "inactive" rheumatic heart disease. However, from the clinically studied group, it will be seen later that 58 per cent of the total number of patients had recognizable rheumatic activity. This indicates that perhaps 600 or more patients of our composite group had rheumatic fever.

For comparison with this figure, we consulted the records of the Surgeon's Office, Mediterranean Theater of Operations, United States Army,* for the actual number of cases reported. This information was available for the twenty-eight months from January, 1943, through April, 1945, and is shown in Table II. The total of 361 cases indicates, in the light of our study, that approximately one-half of the cases of rheumatic fever were formally reported as such. It is of some further interest that only one death is recorded from rheumatic heart disease and one from subacute bacterial endocarditis. We suspect these mortality data are approximately correct.

TABLE II. RHEUMATIC FEVER REPORTED IN THE MEDITERRANEAN THEATER OF OPERATIONS, UNITED STATES ARMY (JANUARY, 1943, THROUGH APRIL, 1945)

YEAR	JAN.	FEB.	MAR.	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.	TOTAL CASES
1943	6	7	1	7	2	2	9	8	10	10	13	14	89
1944	11	11	20	2	26	18	22	24	18	21	16	22	211
1945	13	13	19	16									61
Total													361

Perhaps the most important single factor in the relatively low incidence of rheumatic fever in this Theater has been the absence in epidemic proportions of streptococcal sore throats and upper respiratory infections in general among the troops in this area. According to the records of the Surgeon's Office, even minor outbreaks of such were much less frequent than would be anticipated in a comparable civilian population.

It is of some interest to compare these figures on incidence with those available for the overseas forces in World War I (1917-1918). Tables III and IV have been compiled from information contained in *The Medical Department of the United States Army in the World War*[3] from the section on Admissions in Europe of White Enlisted Men From April 1, 1917, Through December 31, 1919. It is to be remembered that the number of troops upon which these figures are based probably far exceeded the number involved in the Mediterranean Theater of Operations. Furthermore, the accuracy with which the diagnoses of rheumatic fever and of valvular heart disease were made twenty-five years ago was considerably less than at present. It is reasonable to suspect that many cases of

*We are indebted to Colonel W. S. Stone, Department of Preventive Medicine, for this information.

other now well-recognized types of arthritis and allied conditions were included along with rheumatic fever in the group labelled "acute articular rheumatism." Also, the high incidence of "mitral insufficiency" as shown in Table III suggests that the significance of systolic murmurs at the cardiac apex was overemphasized. In spite of these and other equally obvious discrepancies, the striking disporportion in incidence of these conditions in World War I as compared with this sample of incidence in World War II speaks well for the thoroughness with which subjects with rheumatic fever and those with long-standing valvular disease have been excluded from the overseas forces.

TABLE III. ADMISSIONS IN EUROPE OF WHITE ENLISTED MEN (APRIL 1, 1917, TO DEC. 31, 1919) (ABSOLUTE NUMBERS)

Acute articular rheumatism		5,745
Valvular diseases of the heart		2,122
1. Aortic insufficiency	144	
2. Aortic stenosis	28	
3. Mitral insufficiency	1,418	
4. Mitral stenosis	241	
5. Combined lesions, mitral and aortic	44	
6. Tricuspid lesions	3	
7. Valvular lesions, unclassified	244	
Total admissions (Medical diseases)		702,780

TABLE IV. DEATHS IN EUROPE OF WHITE ENLISTED MEN (APRIL 1, 1917, TO DEC. 31, 1919) (ABSOLUTE NUMBERS)

Acute articular rheumatism	19
Valvular disease of the heart	50
Total deaths (Medical diseases)	29,272

CLINICAL FEATURES

The data which form the basis of the following observations consist of the group of 841 patients whose hospital records and board proceedings were personally reviewed. This represents more than one-half of the total number of known cases in the Theater and hence serves as a reliable index of the main features of rheumatic fever and rheumatic heart disease under wartime conditions in this part of the world.

These cases fall into two main groups (Table V): I, those patients with active rheumatic fever and, II, those with the physical signs of valvular heart disease (rheumatic type) but without demonstrable rheumatic infection.

Active Rheumatic Fever.—There were 488 patients, 58 per cent of the series with clinical or laboratory evidence of active rheumatic fever. In one-half (246 patients) it represented a recurrence or reactivation of previously known

TABLE V. INCIDENCE OF RHEUMATIC FEVER AND OF RHEUMATIC HEART DISEASE (841 CASES PERSONALLY REVIEWED)

I	Active rheumatic fever		488 cases (58.0%)
	(a) Rheumatic heart disease	247 (50.6%)	
	(b) Potential rheumatic heart disease	241 (49.4%)	
II	Rheumatic heart disease (Inactive)		353 cases (42.0%)
	Total rheumatic heart disease		600 cases (71.3%)

infection. In the remainder (242 patients) the present illness appeared to be the initial onset of rheumatic infection in so far as could be determined from the history and from the degree of valvular disease present in those with this complication. The presence of well-marked mitral stenosis, for example, was considered evidence of past rheumatic fever, even though there was no suggestion of such in the history. In this group of 242 patients whose illness originated overseas, no clues were apparent to foretell their rheumatic susceptibility. In view of this it was of some interest to inquire into the immediate circumstances which may have been a factor in initiating the illness. In civilian experience it has been repeatedly shown that by far the most frequent event occurring just before, or concurrently with, the onset of rheumatic fever is streptococcal infection of the upper respiratory tract. Occasionally, however, other episodes, nonspecific in character, may apparently act in a similar fashion, especially in regard to recrudescences of the disease. In this connection and limiting the observations to the group of 242 patients with "primary" rheumatic fever, it is noteworthy that the following events occurred with sufficiently striking relationship to the onset to have been recorded in the routine histories of eighty-eight patients; namely, sore throat (sixty-five instances), injury (ten), severe exposure (five), malaria (three), acute gastronenteritis (two), phlebitis (one), pneumonia (one), and lymphocytic meningitis (one). Likewise, in an appraisal of the precipitating events in the recurrent cases of rheumatic fever, sore throat, injury, severe exposure, and occasionally malaria occurred in approximately the same proportion as the foregoing.

The physical findings in 102 patients (42 per cent) of the group with newly acquired rheumatic fever indicated cardiac involvement, usually of rather mild degree, as would be expected at this age; the majority were in the second decade of life. The remaining 140 patients showed no physical signs of cardiac involvement.

There remain 246 patients in the active rheumatic fever group whose illness represented a recurrence of previously known rheumatic infection. This ratio is in accord with the well-known tendency of the disease to recur, especially under the adverse circumstances of exposure and infection. From the point of view of the Army, our chief interest in scrutinizing this group has been to evaluate certain clues which might have been helpful in excluding them from foreign service. First, 106 of this group had chronic valvular heart disease antedating

their military service and known to the patients as a result of premilitary examinations. Certainly in the majority this should have been promptly suspected by history and recognized by physical examination either at the time of induction or during subsequent examinations in the service. Second, a review of the rheumatic fever history of this group is enlightening in that in addition to the overseas illness, thirty-five of these patients (of whom twenty-one also had rheumatic heart disease) had had rheumatic fever since entry into the service and had been treated for it in Army hospitals in the United States. Notwithstanding this, they were later dispatched overseas, the majority with combat units. In one extraordinary (and we believe exceptional) instance a soldier 20 years of age with known rheumatic heart disease since the age of 12 years was treated three weeks for severe acute rheumatic fever and well-marked chronic valvular heart disease of both the aortic and mitral valves at a station hospital while staging in one of the largest camps in the New York area. Presumably because of pressure from his unit, this soldier was discharged from the hospital in order to accompany his organization overseas. He spent the crossing in the ship's sick bay and on arrival in North Africa was sent directly to a general hospital where he continued to exhibit both clinical and laboratory evidence of rheumatic fever. He was returned promptly to the Zone of the Interior. We have encountered only one other similar instance of a soldier having been allowed to continue to his overseas destination after having been hospitalized for rheumatic fever at the staging area prior to embarkation. The foregoing represents the ultimate in mismanagement of these cases; nevertheless, lesser degrees of such have occurred sufficiently often to warrant emphasis at this time.

Further inquiry into the history of this group revealed that twelve additional patients (seven with known rheumatic heart disease) had had previous rheumatic fever within one year of entry into service, nine patients (five with rheumatic heart disease) had had previous rheumatic fever within two years of entry into service, and sixty others (forty-six with rheumatic heart disease) had given a history of two or more, and, in some instances, as many as six, previous attacks of rheumatic fever. It seems to us, at least in retrospect, that in the majority of these patients their susceptibility to rheumatic fever should have been recognized by history and by physical examination at some stage in their military career prior to their arrival overseas, even though it escaped detection at the time of induction. At least the thirty-five who were actually hospitalized for rheumatic fever in military installations in the United States should have been removed from units destined for foreign service.

The severity of rheumatic fever as it has occurred overseas has been of a mild to moderate degree in the majority of cases. Acute migratory polyarthritis responding to salicylate therapy has been the most frequent clinical feature. Relatively few have shown the manifestations often encountered with the more severe forms of rheumatic fever, especially as seen in childhood. Of these more serious manifestations, congestive heart failure occurred in four, pericarditis in eleven, pleuritis associated with pericarditis in four, pneumonitis associated

with other signs of severe rheumatic fever including a delayed auriculoventricular conduction time of 0.50 second in one, and high-grade heart block of 0.30 second or more in four patients, one of whom under observation later developed complete auriculoventricular dissociation. One patient 24 years of age exhibited typical rheumatic nodules over the bony prominence of the extremities, and one other patient, 23 years of age, had a fourth recurrence of typical Sydenham's chorea. In no instance was a death from rheumatic fever recorded, although it was a complicating feature in the patient whose clinical course was briefly noted in the discussion of post-mortem data in the preceding section.

Rheumatic Heart Disease.—Rheumatic heart disease manifested by the characteristic physical signs of valvular deformity was present in 600 patients (71 per cent) of the clinically analyzed series (Table V). In evaluating the thoroughness of the screening of Army personnel for the purpose of helpful criticism thereof, it is of interest that 273 (or 45 per cent) of this group had knowledge of their valvular disease before induction. In the majority (191 patients) this knowledge was acquired at the time of their childhood rheumatism or at subsequent school examinations; in others (thirteen patients), as a result of insurance or industrial examinations; and by some (twenty-five patients), because they had been rejected on this account by other branches of the Armed Forces before their ultimate induction. In eleven instances the presence of heart disease was recognized at the time of induction but, according to these patients, after considerable discussion and consultation they were accepted. In only two instances did patients state they were accepted without an examination.

Active rheumatic infection discussed in the preceding section was also present in 247 of this group and largely determined the management and disposition of these patients (Table V). There remained, however, 353 patients with chronic valvular disease of the rheumatic type without clinical or laboratory evidence of concurrent rheumatic fever. This group with so-called inactive rheumatic heart disease consisted of those who were hospitalized because of symptoms directly referable to the heart (in 228 instances) and those whose heart disease was recognized as an incidental finding during hospitalization for other unrelated disease or injury (in 125 instances).

The extent of involvement of the heart in 600 patients whose records were available for review is indicated in Table VI. Cardiac enlargement was present in 162 patients (27 per cent). In the majority it was of slight to moderate degree. Valvular disease in this group differed in no significant fashion from that observed in similar series for this age group in civilian practice. For example, in a series of 1,097 patients in New England (White and Jones) in whom valvular disease was sufficient or definite enough to be diagnosed clinically, 56.3 per cent were thought to have mitral valve disease alone as compared with 69 per cent for the present series, 14.7 per cent aortic alone as compared with 12 per cent, and 28.9 per cent both aortic and mitral as compared with 19 per cent here.[4] The relative incidences of uncomplicated mitral stenosis and of slight aortic regurgitation are a trifle greater in this group than is ordinarily encountered, and in like fashion

TABLE VI. RHEUMATIC HEART DISEASE (EXTENT OF INVOLVEMENT IN 600 PATIENTS)

Combined lesions, mitral and aortic		112 (19%)
Mitral involvement		419 (69%)
(a) Regurgitation and stenosis	174	
(b) Regurgitation	145	
(c) Stenosis	100	
Aortic involvement		69 (12%)
(a) Regurgitation (Slight)	41	
(b) Regurgitation (Free)	12	
(c) Regurgitation and stenosis	16	

combined lesions of the aortic and mitral valves occurred less frequently than is commonly noted in similar studies. The explanation for these slight discrepancies we believe is evident. In the first instance it is well to remember that the diastolic murmur characteristic of mitral stenosis is notoriously difficult to recognize by the inexpert, especially if the patient is not examined recumbent and after exercise. Likewise, the soft blowing diastolic murmur best heard along the left sternal border indicative of slight aortic regurgitation is easily overlooked. It is to be expected then that the number of patients with these two isolated lesions which most easily escape detection in hurried examinations would appear relatively more frequently in the group under consideration. Contrariwise, combined valvular lesions are more easily detected and thus the majority should have been eliminated from this series. No instance of tricuspid or of pulmonary valve disease was recognized, and because of their relative rarity it is unlikely that such have occurred.

There remain the 241 patients in the active rheumatic fever group whose heart escaped demonstrable damage (Table V). These are classified as having potential rheumatic heart disease and require no special comment at this time. It is of passing interest, however, that 23 of this group had abnormally long auriculoventricular conduction times of 0.20 second or more by electrocardiogram during their rheumatic fever. In one instance the P-R interval measured 0.30 second. It is to be expected that approximately 25 per cent of this group in the course of months or years will show signs of valvular heart disease.[5]

Complications.—The more serious complications of rheumatic heart disease are auricular fibrillation, congestive failure, embolism, and subacute bacterial endocarditis. The period of overseas hospital observation of the patients in the present series is relatively short, averaging from one to two months, and the majority of the cases represent relatively mild degrees of heart disease as compared with the usual hospital series in civilian practice. Therefore the incidence of these important complications would naturally be low.

Auricular fibrillation was present in eight patients, all of whom had extensive rheumatic heart disease with well-marked mitral stenosis. In none was active

rheumatic fever a factor in precipitating the arrhythmia, and in three instances it was paroxysmal in nature. An additional patient with severe rheumatic heart disease had occasional episodes of paroxysmal auricular tachycardia.

Congestive heart failure occurred in only three patients. It was precipitated by a recurrent episode of rheumatic fever in two instances similar in this respect to the relationship commonly observed in childhood. The third patient was 44 years of age and had been in the Army for twenty-five years. He had well-marked cardiac enlargement with regurgitation and stenosis of both the mitral and aortic valves, undoubtedly of many years' standing. He denied knowledge of existing heart disease. The onset of auricular fibrillation precipitated congestive failure which responded satisfactorily to rest, digitalis, and diuretics. Acute pulmonary edema, the result of flooding of the lungs behind a tight mitral stenosis, so commonly observed in severe rheumatic heart disease in civilian practice, was not encountered in this series.

Embolus from the heart (dilated left auricle) to the peripheral circulation occurred in three patients, all of whom had high-grade mitral stenosis and auricular fibrillation. In the first instance, a soldier, 35 years of age, with known rheumatic heart disease since the age of 22, was brought to the hospital with hemiplegia. The second was a soldier 25 years of age with hemiplegia and aphasia. The third was a soldier 48 years of age with eight years' service, in whom the onset of auricular fibrillation was followed in a few days by an embolus to the popliteal artery. Pulmonary embolus, which may arise from a thrombus in dilated right heart chambers but most often comes from a thrombosed vein in the legs or pelvis from venous stasis secondary to heart trouble, was not encountered in this series.

Subacute bacterial endocarditis occurred in four patients with chronic rheumatic heart disease. In all instances the causative organism was the *Streptococcus viridans*. Two of these patients succumbed in this Theater before they could be evacuated to the Zone of the Interior. Post-mortem examination confirmed the clinical diagnosis in each. The remaining two patients whose illness had been present for approximately one month were transferred to the United States.

Angina pectoris was present in three patients 26, 29, and 44 years of age, respectively, each of whom had free aortic regurgitation. It is of interest that the eldest member of this group had been in the service for twenty-two years and had, in addition to aortic regurgitation, well-marked mitral stenosis and regurgitation.

Cardiac neurosis and neurocirculatory asthenia with predominant cardiac symptoms are notoriously common in combat troops. Knowledge of the presence of a cardiac murmur, no matter how innocuous the latter may be, often serves as the focus of a disabling neurosis. In the patients of this series with rheumatic heart disease, there were thirty-eight with disabling neuropsychiatric disorders. In seventeen of these, the symptoms were largely referred to organs of the body

other than the heart. In the remaining twenty-one, however, the complaints were those of neurocirculatory asthenia in eleven, and more clearly of cardiac neurosis in ten. In none of these was the nature or extent of the valvular disease sufficient to cause symptoms per se.

DISPOSITION

It was the established policy in this Theater that patients with rheumatic fever be returned to the United States. In the course of the present survey, certain deviations from this general rule have been noted in occasional instances, and the follow-up data indicate a sufficiently high incidence of recurrent attacks in those who, for one reason or another, were not evacuated to the Zone of the Interior to support amply the wisdom of the basic recommendation both for the welfare of the patient and the best interests of the Army. In regard to chronic valvular heart disease without active rheumatic fever, the policy was slightly more elastic in that those with minimal lesions and no cardiac symptoms were, in some instances, retained in the Theater, usually in a limited service capacity, and, under special circumstances, were even returned to full duty. In Table I we have included the disposition figures for the composite group of patients (those with rheumatic fever and rheumatic heart disease) from the general hospitals. It will be noted that 87.6 per cent were returned to the Zone of the Interior, 6.1 per cent were reclassified for limited service and retained in the Theater, and the remaining 6.3 per cent were returned to full duty. As is evident from Table I, the disposition policy of the various hospitals varied slightly from one extreme, illustrated by that of the 45th General Hospital, where all patients with either rheumatic fever or inactive rheumatic heart disease were automatically returned to the United States to another, illustrated by that of the 37th General Hospital, where only 67.6 per cent were returned to the Zone of the Interior. There was a grand total of 30,193 patients boarded for the Zone of the Interior from the medical service of the general hospitals listed in Table I. This figure includes all neuropsychiatric patients as well as a few with primarily surgical conditions. In spite of the distortion due to the factors noted in the foregoing, rheumatic fever and rheumatic heart disease accounted for 3.9 per cent of the total.

Disposition of the 353 patients with inactive rheumatic heart disease from the personally reviewed series was as follows: to the Zone of the Interior, 273 patients (77 per cent); to limited service, forty-nine patients (12 per cent); and to full duty, thirty-one patients (11 per cent). Those who were returned to full duty had very mild valvular lesions which were discovered incidentally during hospitalization for unrelated disease or injury, and in the majority of those assigned to limited service, the cardiac findings were minimal and not the limiting factor. There is no evidence, in so far as this study is concerned, that harmful effects have resulted in this small group of patients with minimal and inactive valvular disease as a result of their retention overseas. Nevertheless it was recognized that they were potential candidates for recurrent rheumatic fever and, to a lesser extent, for bacterial endocarditis.

CONCLUDING REMARKS

The "*line of duty*" status for this group of patients is of importance, for a considerable number may be expected with the passage of years to become cardiac invalids. In this connection there has been considerable variation in the criteria adopted by the different hospitals. In general, however, for those patients who developed rheumatic fever after entry into the service, irrespective of whether or not they had had previous attacks, the illness was considered "in line of duty." The group of patients with inactive rheumatic heart disease presented a more difficult problem and the policy of the different hospitals varied considerably on this score. In the absence of active rheumatic fever and if the history revealed an attack prior to entry into the service, or if the patient had knowledge of the existence of previous valvular disease, or if the physical signs indicated an advanced lesion which, from clinical experience, is known to require a minimum of several years to develop (for example, high-grade mitral stenosis) and the patient's Army service was of only one to two years, under any of these circumstances most of the general hospitals considered the valvular disease to have existed prior to entry into the service, even though it was not noted at the time of induction and hence was considered not "in line of duty." Whether or not this decision will be upheld when the question arises in the future will undoubtedly depend on the policy adopted at that time by the Veterans' Administration. The most difficult situation for a fair appraisal involved those patients with a relatively short Army career who developed acute rheumatic fever in the service but whose valvular disease by clinical judgment must have existed for many years. In these instances the policy followed by most of the hospitals was to consider the "line of duty" of the rheumatic fever as "yes" and of the advanced valvular disease as "no."

In reviewing the data recorded herein and from the personal experience in this Theater of those especially interested in the problem, as well as from the available data published from other Theaters,[6] it is evident that the recommendations and the measures in force to exclude from overseas service individuals with chronic valvular disease and those especially susceptible to rheumatic fever have been highly effective. This conclusion is amply supported by a comparison with the experience from World War I. That mistakes have occurred is inevitable in view of the urgency which total war precipitated upon the nation. Our sole purpose in stressing the more obvious errors which in retrospect have come to our attention is of a constructive nature and can in no way detract from the superb effort and success of all concerned in excluding the majority of these patients from the Armed Forces.

Finally, and again in retrospect, if all of those with known heart disease and those who had had rheumatic fever within one year of entry into the service had been excluded, the problem presented to the Army in this Theater would have been reduced by 37 per cent. If, in addition, those patients who had a history of two or more attacks of rheumatic fever had also been excluded, this figure would be increased to 43 per cent. This represents perhaps an ideal but impractical solution in the face of a war for survival.

SUMMARY AND CONCLUSIONS

A survey has been made of the incidence, clinical features, and disposition of rheumatic fever and rheumatic heart disease in Army personnel in the North African and Mediterranean Theater of Operations from the original landings in November, 1942, through the Tunisian, Sicilian, and Italian campaigns to the end of hostilities in May, 1945.

1. Reliable statistical data drawn largely from the experience of the seventeen general hospitals in this Theater indicate that approximately 1,400 patients have been hospitalized, of whom more than one-half had active rheumatic fever and the remainder, inactive rheumatic heart disease.

2. A review of the protocols of 1,507 consecutive post-mortem examinations disclosed thirteen instances of healed rheumatic valvular disease of minimal extent and two instances of active rheumatic carditis, an incidence of 9.9 per 1,000.

3. The clinical features of rheumatic fever and valvular heart disease in a series of 841 patients whose records were personally reviewed reveals that 58 per cent had active rheumatic infection and the remaining 42 per cent, inactive valvular disease. The latter was discovered in the majority as an incidental finding during hospitalization for unrelated disease or injury. The initial onset of rheumatic fever appeared to have originated in this Theater in 242 (50 per cent) of those with active disease.

4. In those in whom valvular disease was found, this complication was, in general, of a mild to moderate degree, and its existence prior to military service was known to 45 per cent of the group. Of the more serious complications, auricular fibrillation was present in eight patients, congestive heart failure in three, embolism in three, and subacute bacterial endocarditis in four.

5. The established policy in this Theater was that all patients with rheumatic fever be evacuated to the Zone of the Interior. In regard to inactive rheumatic heart disease of minimal degree, the policy was more elastic. In the present survey it was found that 92.8 per cent of those with rheumatic fever had been returned to the United States, 3.7 per cent reclassified for limited service, and 3.5 per cent returned to full duty. Comparable figures for those with inactive rheumatic heart disease were 77 per cent, 12 per cent, and 11 per cent, respectively.

6. Rheumatic fever and rheumatic heart disease accounted for 3.9 per cent of 30,193 patients boarded for the Zone of the Interior from the medical service of the general hospitals in the Theater.

7. As a result of this survey, which is supported by published data from other Theaters, it is evident that the measures now in force to exclude from foreign service individuals with chronic valvular disease and those especially susceptible to rheumatic fever have been highly effective.

8. In retrospect, if those patients with known heart disease and those who had had rheumatic fever within one year of entry into the service had been

excluded, the problem presented to the Army in this Theater would have been reduced by 37 per cent.

The interest and advice of Colonel Perrin H. Long, Medical Consultant to the Surgeon, Mediterranean Theater of Operations, United States Army, made possible this study. The chiefs of the medical service of the general hospitals in the Theater rendered invaluable aid by consultation and by letter.

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NOTES ON THE SIMILARITY OF QRS COMPLEX CONFIGURATIONS IN THE WOLFF-PARKINSON-WHITE SYNDROME

GEORGE E. BURCH, M.D., AND J. LEROY KIMBALL, M.D.
NEW ORLEANS, LA.

IN THE Wolff-Parkinson-White syndrome the QRS complexes vary in the standard leads and have a tendency to repeat their configurations with considerable frequency. It is the purpose of this paper merely to indicate these various patterns and to give some possible explanations. The significance of these variations is not completely understood. It is intended to call to the attention of others this tendency of the patterns of the QRS complexes in the Wolff-Parkinson-White syndrome to fall into fairly definite groups so that additional data concerning them may be accumulated with the idea of better understanding the nature and significance of the syndrome. Furthermore, the QRS configurations often resemble electrocardiograms seen in conditions which are of a serious nature and which may be confused with the less serious Wolff-Parkinson-White syndrome. Complete left bundle branch block is one serious condition that has been erroneously diagnosed when the true state was the Wolff-Parkinson-White syndrome (Fig. 3). It is important that such errors be avoided.

The electrocardiograms available for study in this laboratory and in the literature reviewed[1-32] contained few precordial leads. For that reason the present report is limited to the standard leads.

All of the electrocardiograms presented the criteria for the diagnosis of the Wolff-Parkinson-White syndrome. In summary these were (1) shortening of the P-R interval (the P-R segment in particular) and a prolongation of the QRS duration with slurring and notching; (2) absence of any clinical signs of heart disease in most instances; (3) occurrence of repeated paroxysms of tachycardia; and (4) return of the electrocardiogram to normal on parasympathetic depression and exercise, as well as spontaneously.

For the purpose of this discussion, the features of the configurations of the QRS complexes of the electrocardiograms evident during the period of aberrant conduction are divided into five types. They are as follows:

Type I.—The QRS complex on first glance appears to be fairly normal. In Lead I the QRS abnormality is limited to the initial portion. It is slurred and otherwise slightly deformed near the isoelectric line. The QRS complexes in this lead consist almost entirely of an R wave of great magnitude. The QRS complex in Lead II shows initial slurring near the base line, while that in Lead III

From the Department of Medicine, Tulane University School of Medicine, and Charity Hospital, New Orleans, La.
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is abnormally wide but not necessarily slurred or deformed. There may be slight left-azis deviation (Fig. 1).

Type II.—There is marked left-axis deviation of the QRS complex. The QRS complex in Lead I consists mainly of an R wave of great magnitude, while

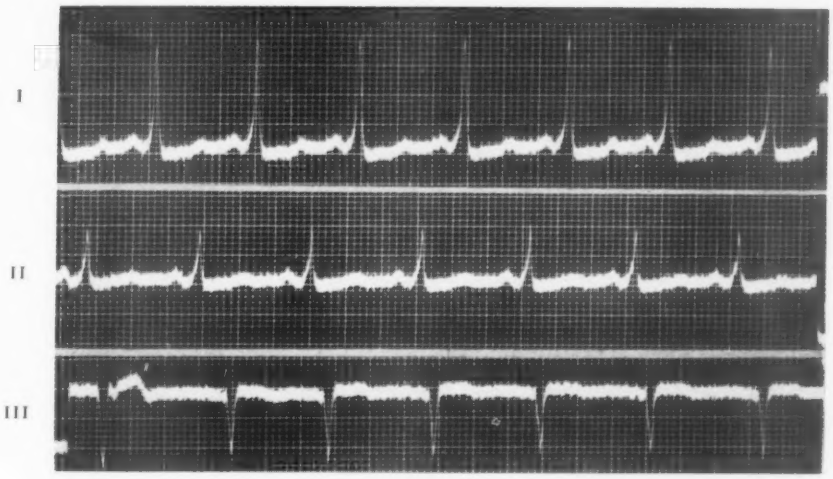


Fig. 1.—Type I pattern with slight deformation limited to the initial portion of the QRS complex.

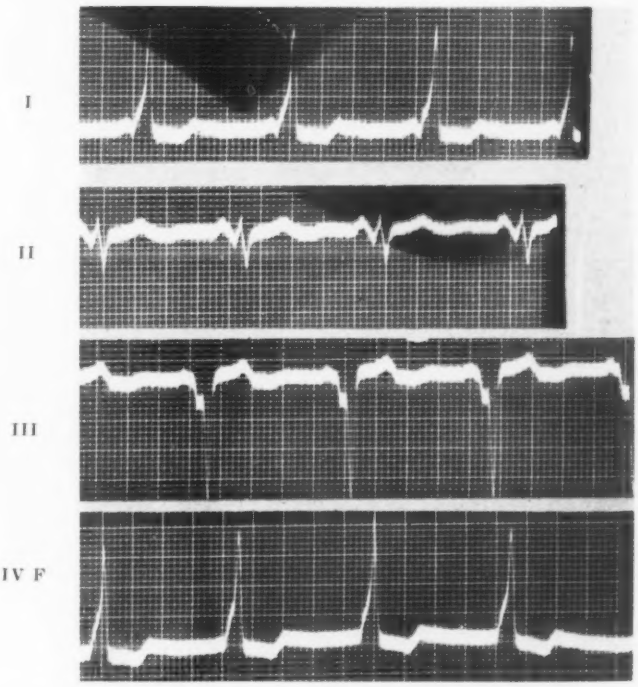
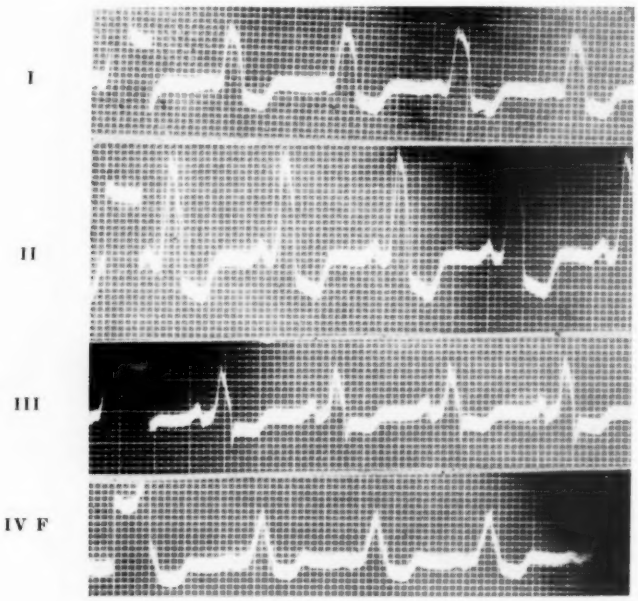
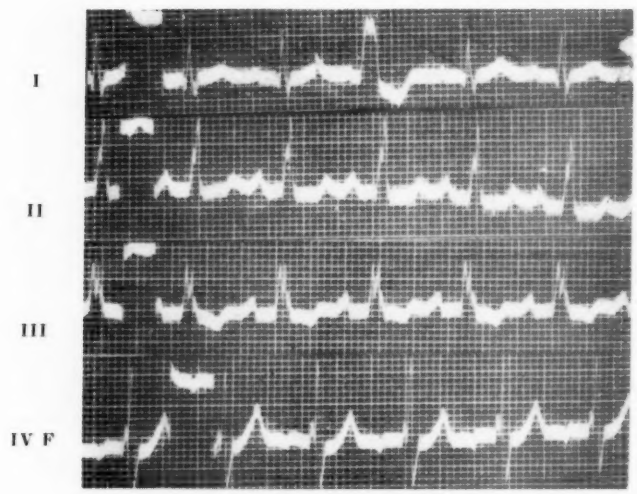


Fig. 2.—Type II pattern with marked left axis deviation of the QRS complex.

in Lead III, an S wave of great magnitude is the conspicuous feature. The QRS in Lead II consists of an R and S wave of relatively low but equal amplitude. There is slurring and various deformations of the QRS complex in Leads I, II, and III. Those abnormalities may not be as obvious in Lead II as in the other leads. A typical tracing is shown in Fig. 2.



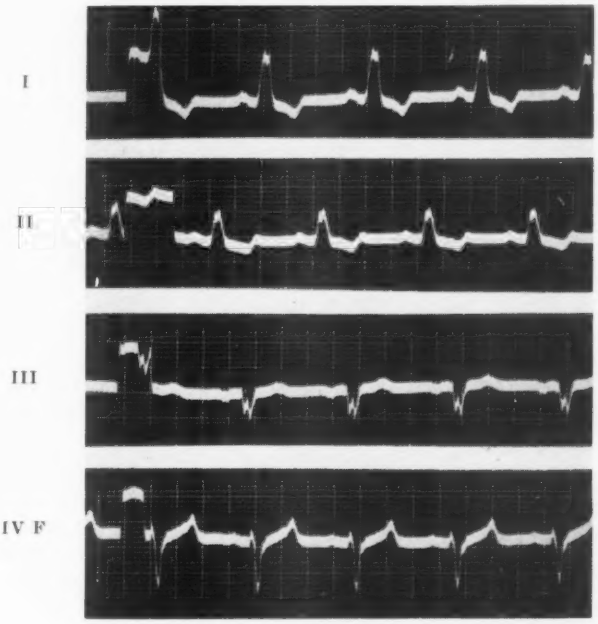
A.



B.

Fig. 3.—Type III pattern resembling left bundle branch block.

Type III.—The pattern of the QRS complex in all standard leads, and, of course, particularly in Lead I, resembles very closely complete left bundle branch block. The resemblance to left bundle branch block is so marked that it is very easy to overlook the syndrome. The short P-R interval suggests the correct entity. The QRS complex is slurred and variously deformed throughout its duration; the slurring and notching is not limited to the first part of the complex. As in true complete left bundle branch block, the main deflection (the one of greatest duration) of the QRS complex in Lead I is upright (Fig. 3).



C.

Fig. 3 (Cont'd).—*For complete legend ,see opposite page.*

Type IV.—In this type the QRS pattern in Lead I resembles true complete right bundle branch block. The terminal portion of the QRS complex is an S wave of great duration. It is this portion of the QRS complex that is especially slurred and deformed. A slurred R wave of low amplitude in Lead I is usually present. The QRS complexes in Leads II and III are deformed terminally as well as initially. There have been only a few such types reported in the literature, none having been encountered by the authors personally. Fig. 4 is a typical illustration of this QRS pattern. A case reported by Vakil[30] appears to be a true right bundle branch block rather than a Wolff-Parkinson-White syndrome.

Type V.—This group consists of QRS patterns of *normal duration* in all three standard leads. The short P-R interval in all leads suggests the correct syndrome. If patients with such electrocardiograms are followed, subsequent

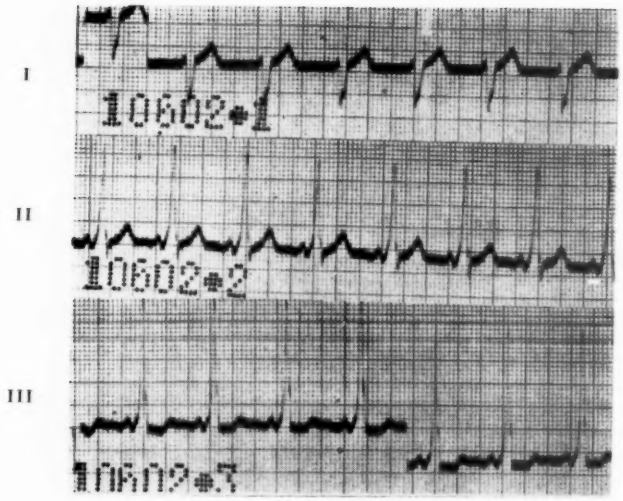


Fig. 4.—Type IV pattern resembling right bundle branch block.

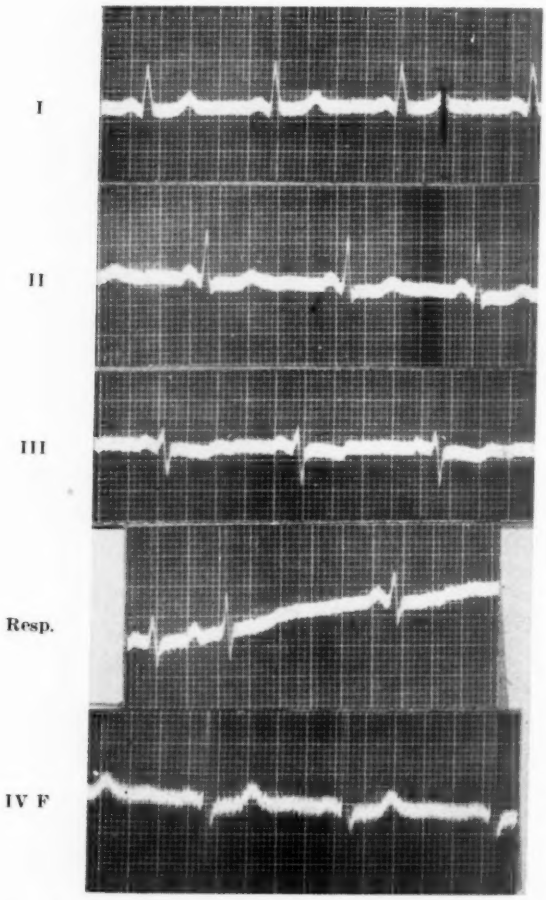


Fig. 5.—Type V pattern with the QRS complexes of normal duration in all leads suggesting essentially normal order of ventricular depolarization.

tracings may show the P-R interval to revert to normal and the QRS complex to alter its configuration simultaneously. The cases reported by Fox[31] and by Öhnell[34] are the only examples of such an electrocardiogram encountered in the literature. In our personal experience one (questionable) similar electrocardiogram was noted (Fig. 5). The second cardiac cycle of Lead III during deep inspiration (Fig. 5) was initiated by an auricular ectopic focus. This resulted in a normal P-R interval and a change in the order of ventricular depolarization indicated by the change in the QRS complex to a more normal appearance. This is in support of the Wolff-Parkinson-White syndrome. Although the QRS complex in this fifth type is of normal duration, it may or may not be recognizably deformed. When there are only slight changes in the order of ventricular depolarization and the resulting deformity is minimal, this slight deformity is earily recognized when the mechanism reverts to normal and the normal QRS complex becomes apparent.

DISCUSSION

It is generally agreed that the Wolff-Parkinson-White syndrome is produced by an anomalous connection (cardiac muscle or neuromuscular pathway) between the atria and the ventricles.[6,9,11] This results in an early activation of ventricular depolarization. The order of depolarization begins, at least, in an abnormal fashion. The site of initiation is determined by the site of connection of the anomalous pathway to the ventricle. As far as the initiation of ventricular depolarization is concerned, the net result is similar to the initiation of ventricular depolarization by an impulse originating in an ectopic focus in the ventricular musculature as in ventricular ectopic beats. In the case of ventricular premature contractions, ventricular depolarization is not completed by an impulse entering the Purkinje system later from the atrioventricular node as is the case in the Wolff-Parkinson-White syndrome. It is well to remember that combination complexes (QRS) may even resemble those of the Wolff-Parkinson-White syndrome if an ectopic focus in the ventricles initiates ventricular depolarization late in the cardiac cycle and the normal impulse from the auricle enters the ventricle from above via the normal pathways to complete ventricular depolarization. The number of sites of origin of ventricular depolarization in ventricular premature contractions is unlimited, and the resultant variations in configurations in the recorded QRS complexes are likewise unlimited. This is essentially true also for the Wolff-Parkinson-White syndrome. However, in this syndrome, because of the nature of the anomalous pathway, the ventricular terminus (anatomic and electrical) is near the base of the ventricle (it is quite unlikely, though conceivably possible, for the anatomic and electric terminus to be near the apex of the heart). For that reason the initial process of ventricular depolarization in the Wolff-Parkinson-White syndrome should resemble in all respects the initial process of a ventricular premature beat initiated by an ectopic focus located in the base of the ventricle which is the site of termination of the anomalous pathways. The records in the completed electrocardiograms should resemble each other.

The order of depolarization and the configuration of the QRS in the completed electrocardiogram is also influenced by the relation of the site of termination of the anomalous pathway to the epicardial and endocardial surfaces.

From the foregoing discussion, it is obvious that the QRS patterns in the Wolff-Parkinson-White syndrome should bear a relation to the QRS patterns in ventricular premature contractions. If the anomalous pathway ends in the right ventricle, the initial slurred portion of the QRS complex is upright in Lead I. In the studies of Rosenbaum and associates[9] the slurred abnormal portion of the QRS complex in Lead I was found to be upright and the anomalous pathway was found to terminate in the base of the heart more in the right half of the muscle mass. Wood and Wolferth[20] were fortunate enough to study histologically the heart of a patient who in life had an electrocardiogram presenting the Wolff-Parkinson-White syndrome. The slurred and deformed portion of the QRS in Lead I was upright and the serial sections of the heart showed the anomalous pathway to terminate in the base of the right ventricle. Öhnell[34] also found an anomalous band of muscle connecting the left atrium to the left ventricle near the interventricular septum. The electrocardiogram, as would be expected, resembled that of Type V discussed.

The fact that the QRS configurations in the Wolff-Parkinson-White syndrome fall into five types may be fortuitious in view of the fact that there are not many such cases available for analysis. It is quite possible, however, for the site of termination of the pathways to be fairly constant. Not until many electrocardiograms and much autopsy material have been accumulated will this be understood.

The configurations of the QRS depend upon the order of ventricular depolarization. In the Wolff-Parkinson-White syndrome the QRS complex is essentially a combination complex, as mentioned previously. There is a force of depolarization produced by a depolarization process initiated in the ventricles at the terminus of the anomalous pathway and another force of depolarization produced by a depolarization process in the ventricles initiated in a normal fashion in the remaining polarized resting muscle by an impulse reaching the ventricle via the A-V node and Purkinje system. It is obvious that the relative times of initiation and duration of these two processes of depolarization will influence the qualities of the forces involved and the configuration of the QRS complexes in the completed electrocardiogram. For example, if an anomalous pathway terminates in the base of the right ventricle, an impulse entering this pathway will initiate depolarization of the right ventricle. Because of the position of this ventricle in relation to the right-arm and left-arm electrodes of Lead I, an abnormally shaped QRS complex with relatively small manifest magnitude is inscribed in the completed electrocardiogram. Should the A-V node delay the normally progressing impulse from the S-A node for 0.15 or 0.16 second, sufficient time will have elapsed for practically all of the free wall of the right ventricle and most of the septum completely to be depolarized by the aberrant impulse. Now, when the normal impulse enters the ventricle, the depolarization process

is not only completed in a more or less normal fashion, but a marked left-axis (mean) deviation of the QRS complex results. This marked left-axis deviation is to be expected since the electromotive force created by the depolarization process in the left ventricle exists almost alone or alone; that is, free from any neutralizing influences by forces of depolarization in the right ventricle which has already been depolarized from the anomalous pathway. Because of the mass of muscle in the left ventricle and the position of the wall of this ventricle in relation to the right-arm and left-arm electrodes of Lead I, the manifest magnitude of the QRS axis is great terminally. This reasoning offers an explanation for the Type II QRS complexes (Fig. 2). A study of the cases reported in the literature in which electrocardiograms were taken with and without conduction through the anomalous pathways support the foregoing explanation.[9,11-21]

In the Type I (Fig. 1) QRS pattern, the delay of the impulse from the auricles by the A-V node must be relatively short (about 0.15 second in most instances) so that the process of ventricular depolarization initiated via the anomalous pathway is of relatively short duration; under these circumstances most of ventricular depolarization is initiated via the impulse from the A-V node. From a study of the cases with and without function of the anomalous pathway reported in the literature, this appears to be true.[1-8]

This same argument can explain the QRS configurations of Types III and IV (Figs. 3 and 4). In order for the slurring and various types of deformities in the QRS complexes to occur throughout or almost throughout the duration of the QRS complex, the depolarization process initiated at the terminus of the anomalous pathway must progress through all or most of the ventricles uninfluenced by another depolarization process initiated by an impulse traveling in a normal fashion via the A-V node. This would occur if the A-V node conduction at the time were relatively slow, 0.18 second or longer. The influences of digitalis[33] in delaying A-V conduction and increasing the duration of the depolarization process initiated via the anomalous pathway is in support of the foregoing argument. If this be true, the QRS complexes should closely resemble ventricular premature contractions. Impulses entering the right ventricle via an anomalous pathway should resemble right ventricular premature contractions. In fact, the QRS complexes with the main deflections positive in all three standard leads in Fig. 3 and with the secondary type of T wave changes have the characteristics of right ventricular premature contractions initiated by a focus in the base of the right ventricle. Similarly, the QRS complexes in Fig. 4 resemble left ventricular premature contractions.

In support of the idea of relatively delayed A-V conduction explaining tracings of Types III and IV, Figure 3, *A* is shown. In this figure the P-R interval during the normal mechanism is from 0.18 to 0.20 second. When this time interval is measured after the beginning of the P waves in Fig. 3, it is noted that an impulse could not have entered the ventricles until they were almost completely depolarized by means of the then functioning anomalous pathway. In fact, by 0.18 to 0.20 second from the beginning of the P waves of Fig. 3 the

ventricular musculature is so completely depolarized that the muscle could not even respond to a stimulus that might present itself via the A-V node. A study of tracings of Types III and IV reported in the literature for periods of functioning and nonfunctioning anomalous pathways showed P-R intervals or A-V delays which support the foregoing argument.[22-30]

The importance of timing of the two depolarization processes in Wolff-Parkinson-White syndrome is evident. The marked tendency for A-V node conduction (P-R interval) to vary in health and disease and under the influence of drugs is well known. In view of the marked variations in the delay of auricular impulses in the A-V node, it is not surprising that upon this basis alone the QRS complexes in Wolff-Parkinson-White syndrome should be so variable and a QRS tracing of Type I should change to one of Type III. If the matter of timing were the only important factor concerned with the production of variations in the QRS configurations, it would be possible to classify the configurations of the recorded QRS complexes on relative timings of impulse conduction via the anomalous and A-V node pathways. There are, however, several other factors of importance which can influence the configuration of the QRS complexes. The integration of such factors as anatomic rotation of the heart, multiple pathways functioning simultaneously or separately which terminate in various portions of the ventricle, along with variations in delay in A-V conduction, certainly must contribute to the variations in the QRS pattern from patient to patient or from moment to moment within the same patient.

From the configuration of the QRS complexes in the standard leads, it is possible to have only a general impression of the site of termination of the pathways. In Type V (Fig. 5) the QRS complexes are of normal duration and may or may not be recognizably deformed. The rather normal or normal-appearing QRS complex during the abnormal mechanism indicates a fairly normal order of ventricular depolarization. For the order of ventricular depolarization to be about normal, the abnormal pathway must have terminated in the interventricular septum near its base, in the bundle of His, or in either of the main branches near the bundle of His. Such an anatomic termination of the anomalous pathway is quite possible and is a probable explanation for the Type V tracing (Fig. 5). The finding in Öhnell's patient of a QRS complex of normal duration and only slight deformation and on serial section a short (6 mm. in length) anomalous bundle terminating near the base of the left ventricle near the septum is certainly in support of the hypothesis presented to explain the Type V tracings.

Finally, the tendency for QRS patterns to repeat themselves is pointed out not for the purpose of recommending that the tracings be so classified for clinical purposes, but merely to indicate this tendency in order to lead to a better discussion and presentation of some of the physiologic concepts of the Wolff-Parkinson-White syndrome. Öhnell[34] has made an extensive and detailed study of the various electrocardiographic patterns and has classified them on their configurations rather than on the electric events responsible for them. Obviously, if one considers minute details of configurations of the electrocardiograms,

the patterns can show unlimited variations. The five general types discussed reduce the configurations to more practical levels. Minute detailed descriptions based upon empirical rules seem to add little at this time.

SUMMARY

1. The tendency of the QRS configurations in Wolff-Parkinson-White syndrome to fall into five types is pointed out.

2. An analogy between the initiation of ventricular depolarization by the terminus of the anomalous pathway and a similarly located focus of a ventricular premature contraction is drawn.

3. An electrocardiogram of a questionable case of Wolff-Parkinson-White syndrome with normal-appearing QRS complexes is presented in Fig. 5. It is suggested that these QRS complexes were initiated by impulses reaching the ventricles via an anamalous pathway terminating in the center of the septum near its base or in the bundle of His.

4. Theoretic explanations are offered for the QRS patterns observed in the Wolff-Parkinson-White syndrome.

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THE SYNDROME OF ABDOMINAL AORTIC ANEURYSM RUPTURING INTO THE GASTROINTESTINAL TRACT

Summary of the Literature and Case Report

Homer H. Hunt, M.D., and Carl V. Weller, M.D.
Ann Arbor, Mich.

RUPTURE of an aneurysm of the abdominal portion of the aorta into the gastrointestinal tract is accompanied by a characteristic syndrome which will usually suggest the diagnosis. This dramatic accident is sufficiently rare to justify the continued reporting and collection of cases for analysis. In this paper, another example of the rupture of such an aneurysm into the duodenum is recorded, and the list of reported cases is brought up to date.

Including the one reported here, forty-one cases have now been collected. Undoubtedly others are concealed in the numerous studies of aortic aneurysm in general. In 1943, Rottino,[1] in a very thorough search, found thirty-one examples of rupture of an abdominal aortic aneurysm and added a case of his own. The essential clinical and morphologic data concerning the group, so far as they were obtainable, were arranged by him in tabular form. Our Table I, adding nine cases, is purposely constructed as a continuation of that presented by Rottino, using the same headings and continuing his serial numbering. Since the cases reported by Nunneley[2] and Peñas[3] were not known to Rottino, his own case becomes the thirty-fourth in the series. References to the cases in Rottino's table will not be repeated except that for Vehling,[4] whose dissertation, available in microfilm, can now be cited more accurately.

Probable examples, which do not qualify for inclusion in Table I because perforation was impending rather than actual, or because it is not clear that the aneurysm was primarily aortic, can be found among studies reported from other points of view. Washburn and Wilbur[5] described obstruction of the third portion of the duodenum by an aneurysm of the abdominal aorta. The patient was a woman, aged 67, with a large, pulsating, epigastric mass. There had been no blood in the vomitus, but later there was a slight trace of blood in a test meal and occult blood in the stools. Rupture must have been impending in this case. The clinical diagnosis was confirmed when a posterior gastroenterostomy was performed for the relief of obstruction.

In an analysis of the symptoms and signs in a group of twenty-four cases of abdominal aneurysm, Eliason and McNamee[10] found massive hematemesis and melena each mentioned once. Although pain was the predominant symptom in

From the Department of Pathology, University of Michigan.
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TABLE I. AORTIC ANEURYSM RUPTURING INTO THE GASTROINTESTINAL TRACT

NO.	DATE	AUTHOR	AGE	SEX	PERTINENT HISTORY LEADING TO ADMISSION	CLINICAL OBSERVATIONS	COURSE	PATHOLOGIC CHANGES
32*	1906	Nunneley[2]	28	M	Pain in epigastric region	Pulsating tumor below ensiform cartilage	Two months after admission, hematemesis and death	Saccular aortic aneurysm above origin of celiac axis; perforation into left side of anterior portion of duodenum
33	1941	Peñas[3]	62	M	Pain in lumbar and right inguinal regions	Tumor mass in umbilical region	Sixteen days after admission, sudden weakness, rapid pulse, hematemesis, unconsciousness, and death in six hours	Massive gastrointestinal hemorrhage; saccular aortic aneurysms arising below superior mesenteric artery rupturing into third portion of duodenum
34	1943	Rottino[1]	53	M	"Arthritis" of right hip, epigastric pain	Pulsating mass with bruit in epigastrium	Sudden hematemesis, melena, and death in two days	Saccular aortic aneurysm below renal arteries rupturing into third portion of duodenum
35	1943	Howland and Sprofkin[6]	59	M	Pain in left upper quadrant for six weeks	Albuminuria, then anuria	Sudden "shock" with ashy pallor; death three days after onset of anuria	Saccular aortic aneurysm at level of superior mesenteric artery, compressing left renal vein and rupturing into third portion of duodenum
36	1944	Hiller and Johnson[7]	76	M	Epigastric pain for five weeks	Occult blood in stools	Found semicomatose with dark red liquid feces in bed; death forty minutes later	Saccular aneurysm 6.5 cm. above aortic bifurcation, rupturing into jejunum 2 cm. below duodenum

37	1944	Morison[8]	64	F	Aching pain on both sides of abdomen; frequent scalding micturition	Pulsating tender mass to left of umbilicus	After ten weeks, severe hematemesis and death in seven hours	Saccular aortic aneurysm just above inferior mesenteric artery; rupture into third portion of duodenum
38	1944	Pratt-Thoma	31	M	Epigastric pain for three months; collapsed while walking; hematemesis	Visible pulsating mass above and to right of umbilicus	State of "shock"; death in two hours; profuse hemorrhage from rectum	Saccular aneurysm at level of celiac axis and superior mesenteric artery; perforation into duodenum, 20 cm. below pyloric ring; stomach and intestine filled with blood
39	1944	Pratt-Thomas[9]	48	M	Pain in epigastrium and radiating from lumbar spine; vomiting	Pulsating mass in umbilical region increasing in size	Died suddenly as gastric tube was about to be passed	Saccular aortic aneurysm immediately below mouths of renal arteries; perforation into third portion of duodenum; stomach and intestine filled with blood
40	1944	Pratt-Thomas[9]	52	M	Abdominal pain; hematemesis	State of "shock"; melena	Death seven days after hematemesis	Aneurysmal dilatation of aorta 1 cm. below renal arteries; perforation into overlying duodenum; intestine nearly filled with blood
41	1946	Hunt and Weller	47	M	Entered hospital for pain in right knee	Septic arthritis, acute psychosis	Hematemesis, with death in five hours	Saccular aortic aneurysm 4.5 cm. below superior mesenteric artery; rupture into third portion of duodenum

*Numbered in sequence with cases collected by Rottino.[1]

the group as a whole, reference is made to one patient who had very little pain but did have massive hematemesis from rupture of an aneurysm of the *celiac axis* into the jejunum. Death occurred twenty-four hours after the onset of hemorrhage. This case and one other, attributed to the celiac axis, are excluded from Table I.

Scott[11] included lesions of any abdominal artery in his report of ninety-six cases of abdominal aneurysm. "Massive gastrointestinal hemorrhage followed rupture into the duodenum in one patient." In his table a second patient is recorded as having hemorrhage into the duodenum following rupture. Whether one or both of these were aortic aneurysms is not stated.

A brief account of our case follows.

CASE REPORT

I. B., No. 483037, was an unmarried Swedish bricklayer, aged 47. He was admitted to the University of Michigan Hospital with a painful left knee as his chief complaint. Physical evidences of septic arthritis were present and bone destruction was found roentgenographically. The patient developed an acute psychosis and a reliable history could not be obtained. However, he referred the onset of pain to a period about one month prior to admission. Venereal infection was denied, but exposure six weeks before entry was admitted. Serologic test of the blood (Kahn) was negative on two occasions. The gonococcal complement fixation test of the blood serum was strongly positive. The patient was given sulfathiazole, and three operative procedures for drainage of the left knee were carried out. On the third postoperative day, at 5 A.M., the patient had a sudden hemorrhage from the mouth, amounting to about 300 c.c. of fluid and clotted blood. A medical consultant suggested pulmonary infarction, but roentgenograms of the chest were negative. None was made of the abdomen. At 10:15 A.M. of the same day, the patient had a second hemorrhage and expired.

Autopsy.—At autopsy (A-420-AS), the stomach, duodenum, and entire small bowel were found to be filled with a jellylike blood clot forming a cast of the lumen. In the transverse segment of the third portion of the duodenum there was a small, irregular opening which communicated with a firm, somewhat elastic, retroperitoneal mass. After removing the duodenum and aorta together, this mass was found to be a saccular aneurysm protruding from the right anterolateral surface of the abdominal aorta. The sac measured 6 cm. vertically, 4.5 cm. transversely, and 3.5 cm. ventrodorsally. Its upper border was 4.5 cm. below the orifice of the superior mesenteric artery and its lower border 2 cm. above the iliac bifurcation. The mouth of the sac lay to the right of the inferior mesenteric artery and measured 2.5 by 2 centimeters. The wall of the sac was composed of thick fibrous and calcareous laminae (Figs. 1 and 2). The remainder of the abdominal aorta showed thickening of the wall, loss of elasticity, widening of the lumen, and numerous yellowish-gray, elevated, hyaline plaques against a grayish-white intima. There were also areas of atheromatous "ulceration," but the gross features of syphilitic aortitis were not found.

Sections of all organs were examined microscopically. The heart showed atherosclerotic changes of the coronary arteries and at the bases of the aortic cusps. In the myocardium there were scattered interstitial infiltrations of mononuclear cells, in part eosinophiles, which were thought to be due to the use of sulfathiazole.

The aorta was examined in sections from several levels. In the upper portion of the thoracic aorta, atheromatous changes were of but slight degree. There was a very moderate increase in the blood vessels of the adventitia, about some of which there was a slight lymphocytic infiltration. In the abdominal aorta there were very marked atheromatous lesions of the intima, with deposition of cholesterol and calcareous plaques. The media showed areas of necrosis with fragmentation and ultimate loss of elastic fibers. In the adventitia there were infiltrations of

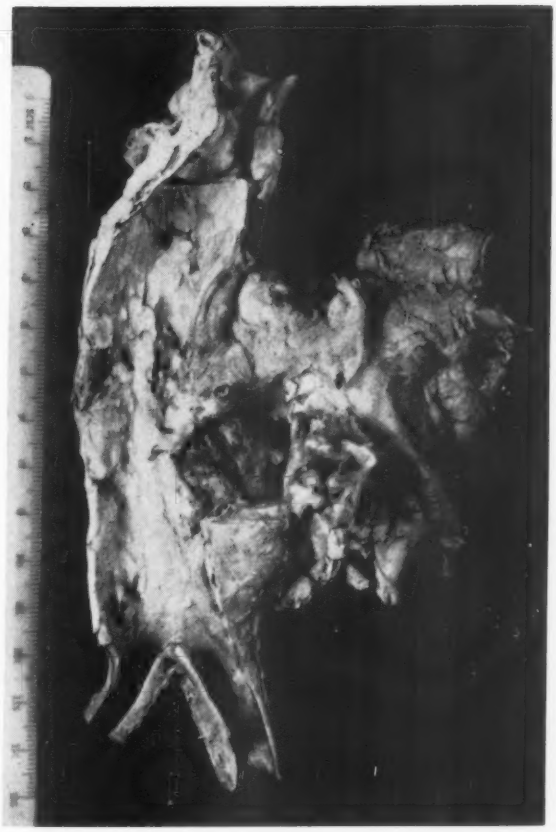

Fig. 1.—The abdominal aorta has been opened approximately along the mid-dorsal line. The mouth of the aneurysmal sac is shown to the right of the opening of the inferior mesenteric artery. The adherent duodenum is largely concealed by the sac of the aneurysm.

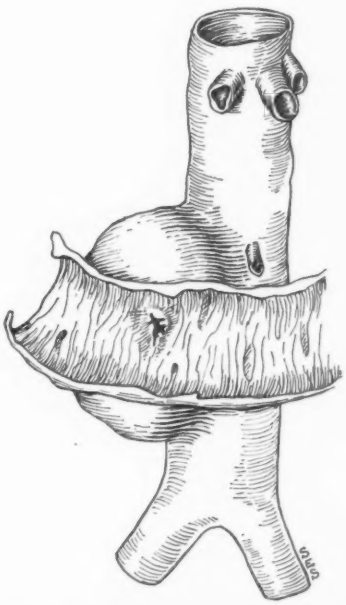

Fig. 2.—This schematic drawing, prepared from a photograph and sketch made at the time of the autopsy, shows more clearly the anatomic relations of the aneurysm. Rupture into the duodenum occurred at the summit of the convexity of the anterior wall of the sac.

lymphocytes and plasma cells, but the changes found were not such as to justify a diagnosis of syphilitic aortitis.

Near the point of perforation of the aneurysm into the duodenum there were organizing, fibrinous peritonitis and necrosis and leucocytic infiltration of the mucosa.

A section of synovial membrane from the left knee showed active chronic pyogenic inflammation with numerous plasma cells. This was considered to be fully compatible with the clinical impression of gonococcal arthritis.

The pathologic diagnoses were: large saccular aneurysm of the abdominal aorta, with rupture into the third portion of the duodenum and massive hemorrhage into the bowel; hematemesis, with aspiration of blood into the lungs; advanced aortic atherosclerosis; organizing fibrinous peritonitis of the duodenum; coronary atherosclerosis; old epicarditis; subepicardial fatty atrophy of the myocardium; left ventricular myocardial hypertrophy; interstitial myocardial infiltrations of large mononuclear cells and eosinophiles (sulfathiazole?); pulmonary congestion and edema; beginning terminal lobular pneumonia; degenerative fatty infiltration of the liver and kidneys; septic arthritis of the right knee (gonococcal?); cholelithiasis.

DISCUSSION

Incidence as to Sex and Age.—This augmented series adds to the earlier emphasis upon the greater liability of men to this syndrome. With thirty-five of forty-one examples in men, a 6:1 ratio is found. The range in age remains unaltered, from 20 to 81 years. While the distribution by decades is fairly uniform between these extremes, correction for total number living would show an increasing incidence beginning with the sixth decade. It can be due only to chance that for four of the thirty-eight patients the age was 28 years. Yet the occurrence of eight cases in the six-year period between 27 and 32 years-of-age emphasizes the importance of this syndrome in a comparatively young group.

Location of the Aortic Aneurysm.—In sixteen cases the level at which the aortic aneurysm had developed was not stated with sufficient exactness to be used in tabulation. Moreover, the large size of many of these aneurysms in comparison to the small distances between successive aortic branches must have rendered exact localization impossible in many cases. Locations were specified as follows: above celiac axis, two cases; at celiac axis, three; above superior mesenteric artery, one; at superior mesenteric artery, one; below superior mesenteric artery, five; above renal vessels, one; below renal vessels, six; below inferior mesenteric artery, two; lower abdominal aorta, one; above aortic bifurcation, three.

Location of Rupture Into Gastrointestinal Tract.—As found by Rottino, the third portion of the duodenum is the portion of the gastrointestinal tract into which perforation of an abdominal aortic aneurysm occurs most frequently. This site was specified, or could be deduced, in twenty-nine of the forty-one cases. In two others, perforation was into the second portion of the duodenum, and in two into the duodenum, without specification as to the portion. Of the remaining cases, five showed perforation into the stomach, two into the jejunum, and one into the small bowel, with the region unspecified. The reasons for the preponderance of perforation into the third portion of the duodenum are anatomic,

depending in part upon the extensive area in which this portion of the duodenum is in relationship to the anterior aortic wall and also upon its firm fixation to the aorta, since the duodenum is retroperitoneal in this portion.

CLINICAL MANIFESTATIONS

The syndrome produced by the rupture of an abdominal aortic aneurysm into the gastrointestinal tract combines the features of abdominal aneurysms in general with those of hemorrhage into the alimentary tract. An accurate antemortem diagnosis may be possible in spite of the rarity of the condition.

For the basic clinical picture of abdominal aortic aneurysm, Kampmeier[12] gave the following as important diagnostic points: presence of an abdominal tumor (60 per cent of all cases); expansile pulsation of the tumor (in 98 per cent of those with tumors); roentgenologic evidence of a calcified abdominal mass, of vertebral erosion, or of an indefinite soft tissue mass (confirming evidence being found by this method in 75 per cent of thirty-two cases in which it was used). With any abdominal aortic aneurysm, death is usually due to hemorrhage, whether the aneurysm is saccular or dissecting. Sometimes death is almost instantaneous, but it may be delayed for hours or days. Lipshutz and Chodoff[13] added to the general picture of abdominal aneurysm the following, as evidence that rupture had occurred: vascular crisis and a state of shock, a high leucocyte count, moderate elevation of diastase content of the urine.

All of the diagnostic criteria summarized by Kampmeier and by Lipshutz and Chodoff apply to the cases of aneurysms in which perforation into the gastrointestinal tract is impending or has occurred. The tumor mass is usually epigastric in position and it is frequently expansile and pulsating. Pain is the chief complaint and may be abdominal or in the lumbar region. Hematemesis and melena are usual terminal features but, as with thoracic aortic aneurysms, there may be a premonitory seepage of blood for days or weeks before the final exsanguinating hemorrhage. This may be discovered through blood-tinged vomitus or as occult blood in the stools. Death may occur immediately, or after a variable interval, following the copious hematemesis or escape of fresh blood from the rectum which completes the diagnostic picture. The report by Manson[14] is typical. "I was called to a passenger train on June 18, 1936, to attend a man who was seriously ill. This man was found to be lying on his back in a first-class lavatory with his trousers down, in a mass of blood and feces. He was blanched and unconscious, and at first sight seemed to be dead." A pulsating tumor was felt in the epigastrium. This patient died five days later and was found to have a saccular aneurysm of the abdominal aorta, which had ruptured into the duodenum. In our own case, hematemesis marked the occurrence of rupture.

There are additional features which may lead the clinician away from the correct diagnosis unless their logical association with this syndrome is recognized. For instance, a high leucocyte count appears to be a constant feature during the period between actual rupture and death. Again, a detailed history of "indi-

gestion" may seem to point so clearly to peptic ulcer that the physical and roentgenographic evidences of aneurysm may be overlooked. The frequency with which an elevated value for urinary diastase will be found has not yet been established but deserves further study. Impairment of renal function has been observed in many instances and depends chiefly upon interference with one or both renal arteries. In the case described by Howland and Sprofkin,[6] in which there was terminal anuria, the mouths of the renal arteries were included in the aneurysmal sac and a thrombus extended into the right renal artery.

SUMMARY

With the new case, which is reported in this paper, forty-one examples of rupture of an aneurysm of the abdominal aorta into some portion of the gastrointestinal tract are known to be available in the literature. In 71 per cent, rupture was into the third portion of the duodenum. The condition has been six times more frequent in men than in women. While the ages were widely distributed, the occurrence of eight cases between 27 and 32 years-of-age indicates the importance of this condition in relatively young patients. The resulting syndrome combines the features of abdominal aneurysm with those of profuse hemorrhage into the gastrointestinal tract. Hematemesis, often with abundant hemorrhage from the rectum, usually marks the onset of the terminal phase.

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AN AURICULAR DIASTOLIC MURMUR WITH HEART BLOCK IN ELDERLY PATIENTS

DAVID A. RYTAND, M.D.
SAN FRANCISCO, CALIF.

IN NINE elderly but ambulatory patients with varying degrees of auriculoventricular block, a blowing murmur was heard at the cardiac apex during ventricular diastole. Phonocardiograms recorded simultaneously with electrocardiograms revealed in each case the vibrations of a murmur, as distinguished from the abrupt auricular sounds so often observed in complete block, and showed the relationship of the murmur to auricular activity. At times, the usual short auricular sounds were also present.

Mitral stenosis did not appear to be present. Calcification of the mitral annulus fibrosus was found in four cases, but this lesion seems not to alter the cardiodynamics as does mitral stenosis and fails to produce an auricular (presystolic) murmur when auriculoventricular conduction is normal.[1]

The purposes of this paper are to report the observations and to discuss the mechanisms which might be responsible for the production of the murmur.

CASE REPORTS

Cases 1 through 4, with calcification of the mitral annulus fibrosus, are the same as those reported in more detail elsewhere.[1] Cases 5 through 9, without calcification, have not been reported before.

CASE 1.—A frail woman 74 years of age, with no history of rheumatic fever, was found to have moderate congestive heart failure and complete heart block. At times, the latter was replaced by 2:1 block and even sinus rhythm with a P-R interval of 0.19 to 0.21 second, but usually the block was complete. Left bundle branch block was occasionally found, and auricular fibrillation complicated complete block for two months. The arterial pressure varied around 200/90. Improvement followed the use of digitalis and diuretics, so that the patient was ambulatory most of the time. She died at the age of 79 years of cerebral vascular disease; necropsy was not permitted. During the period in which the observations recorded below were made, signs of heart failure were virtually absent. The heart did not appear enlarged on physical examination. X-ray examination, however, revealed slight enlargement; the left auricle was not prominent. A nearly complete ring of calcification in the region of the mitral annulus fibrosus was seen fluoroscopically and recorded on films.

There was a loud, coarse murmur during ventricular systole, best heard along the lower left sternal border and transmitted to the apex, aortic area, and carotid arteries. There was no thrill. With complete block, the first heart sound varied in intensity and a blowing murmur in ventricular diastole was heard at the apex. The murmur was enhanced in the left lateral recumbent position. Its position in diastole varied, depending upon the time of auricular activity. The murmur was not heard more than twice in any given diastolic period. When it occurred early in diastole, it was obviously louder than when it occurred later (Fig. 1).

From the Department of Medicine, Stanford University School of Medicine.
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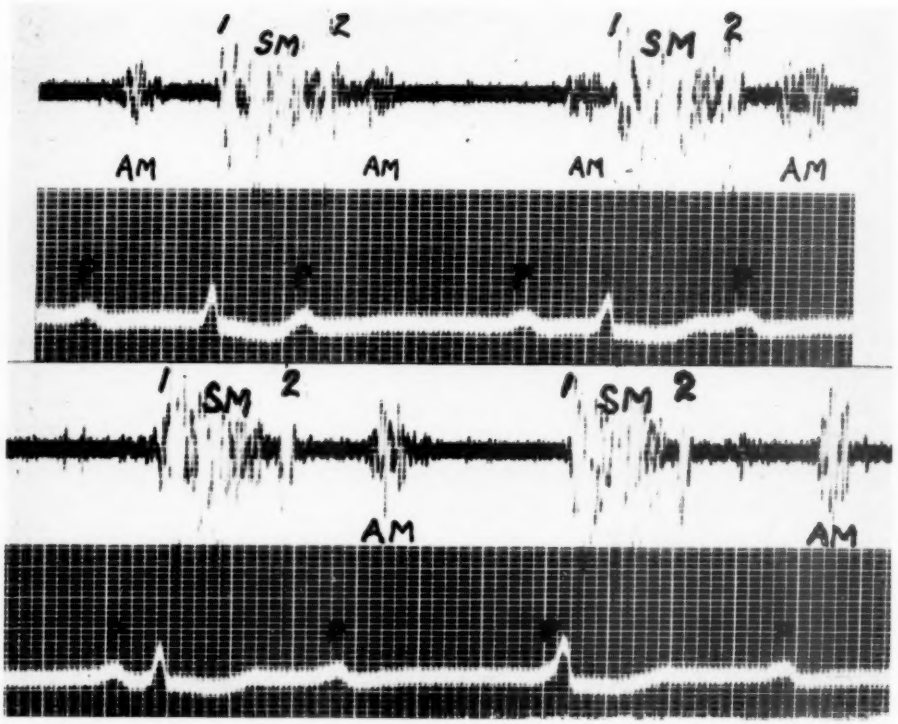

Fig. 1.—Case 1. Simultaneous records of heart sounds at the apex and electrocardiogram. Complete A-V block. Time marking in all figures, 0.04 and 0.20 second. The first and second heart sounds are designated *1* and *2;* the murmur of ventricular systole, *SM*; the auricular murmur, *AM*. Vibrations of the auricular murmur are smaller both early and late in ventricular diastole (upper strip) than at intermediate times (lower strip) and are not recognizable as such with normal P-R intervals (0.17 second in first cycle of lower strip). Small unlabeled vibrations are artefacts. Upper and lower strips are consecutive.

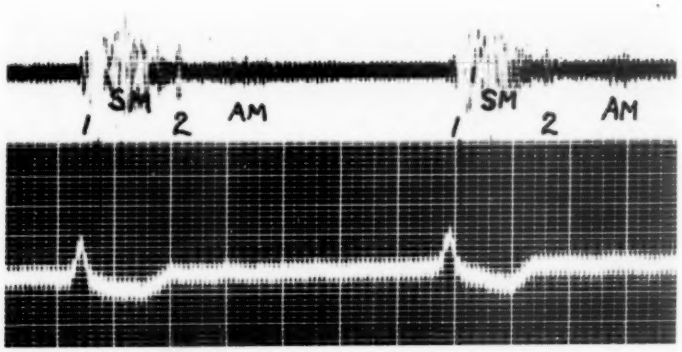

Fig. 2.—Case 1. Same as shown in Fig. 1, but during auricular fibrillation. Small vibrations of murmur, *AM*, are related to the second heart sound.

When 2:1 block was present, the murmur was audible only in the blocked auricular cycle and not well recorded in the conducted one (P-R interval, 0.24 second; preceding R-R cycle, 1.44 second). In the presence of auricular fibrillation, it was faintly audible and recorded early in diastole (Fig. 2). It was not heard during the short periods of sinus rhythm, but unfortunately we were not then aware of the possibility of its existence.

CASE 2.—Dyspnea and angina pectoris in a husky man 68 years of age led to the discovery of calcification in the mitral annulus fibrosus. There was no history of rheumatic fever. After a period of prolonged conduction time, the P-R interval fell to 0.18 second. Digitalis administration was followed temporarily by complete block, then 3:2 block; observations noted in the next paragraph began at this time. Later, even without digitalis, the P-R interval remained fairly constant at 0.30 second. A year later, auricular fibrillation with slow but irregular ventricular response appeared and persisted. Congestive heart failure, starting about the same time, finally led to the patient's death two years after the first examination.

The arterial pressure was 135/90. There were no signs of congestive heart failure. The heart was only slightly enlarged on x-ray examination and the left auricle was not prominent. There was a loud, rough murmur with ventricular systole, loudest at the base but also heard at the apex and over the carotid arteries. There was no thrill. With complete block, a rough, blowing murmur at the apex was audible during ventricular diastole, with behavior similar to that of the murmur described in Case 1. The first heart sound varied in intensity (Fig. 3). When 3:2 block was present, the murmur was not heard with the first of the conducted cycles (P-R interval, 0.24 second), and with such cycles its vibrations were scarcely visible in phonocardiograms; under these conditions the preceding R-R cycle length was 1.38 seconds. With prolonged conduction time (P-R interval, 0.30 second), the murmur was a presystolic one (Fig. 4).

With congestive failure and auricular fibrillation, the left auricle and the heart became dilated. The murmur then became confined to early diastole (Fig. 5), was fainter than when associated with auricular activity, and could not be heard with the patient sitting up.

CASE 3.—An obese woman 68 years of age was found in 1939 to have complete heart block, which persisted until she died of myocardial infarction in 1942. The observations recorded below were made in 1941, when she was seen because of postural vertigo and when she was somewhat dyspneic but ambulatory. There was no history of rheumatic fever. The arterial pressure was 270/110, and peripheral arteriosclerosis was marked. There were no physical signs of congestive heart failure, although there was marked cardiac enlargement. Radiologic study revealed calcification of the mitral annulus fibrosus. The left auricle was not unduly prominent.

A thrill at the base accompanied a loud systolic murmur which was transmitted to the apex and into the carotid arteries. The first heart sound varied in intensity. A soft, blowing murmur was heard at the apex during ventricular diastole; it behaved quite like the similar murmur described in Case 1 (Fig. 6).

At necropsy, the heart weighed 420 grams. The aortic, pulmonic, and tricuspid valves were normal. A band of calcification 1 cm. thick and 9 cm. in circumference encircled the mitral valve in the annulus fibrosus without obstructing the orifice. There was some calcification and distortion of the mitral leaflets near their base, but their free edges and chordae tendineae were normal. There was very slight, diffuse endothelial thickening in the left auricle, without striking enlargement of that chamber. A myocardial infarct was present, and the coronary arteries were diffusely narrowed. Aortic atherosclerosis was marked. Firm masses of calcified fibrous tissue nearly occluded the proximal portions of the innominate and left carotid arteries.

CASE 4.—In 1936, a very small woman 73 years of age developed dyspnea while at the Laguna Honda Home. Study of this symptom led to the discovery of complete heart block; moderate congestive heart failure was present then, but not later.

Examinations subsequent to 1942 revealed advanced peripheral arteriosclerosis. The arterial pressure was 220/70. The heart was somewhat enlarged, its rhythm was regular, and the ventricular rate was 46. There was a rough systolic murmur, faint at the apex, moderate at the left sternal border, and not reaching the carotid arteries.

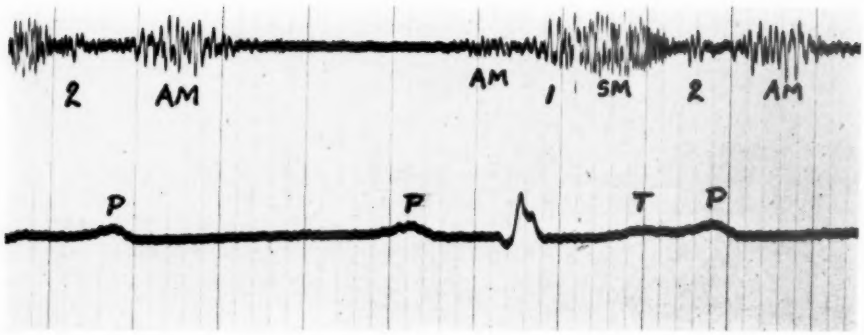

Fig. 3.—Case 2. Same as shown in Fig. 1. Complete A-V block. Vibrations of the auricular murmur, *AM*, are greater early in diastole.

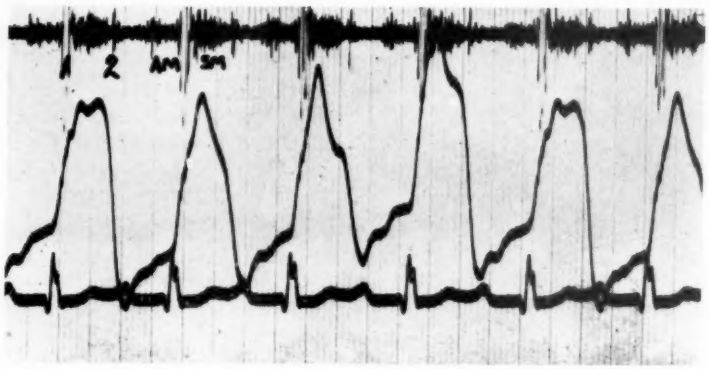

Fig. 4.—Case 2. Simultaneous records of apical heart sounds, apex beat, and electocardiogram. Sinus rhythm; P-R interval, 0.30 second.

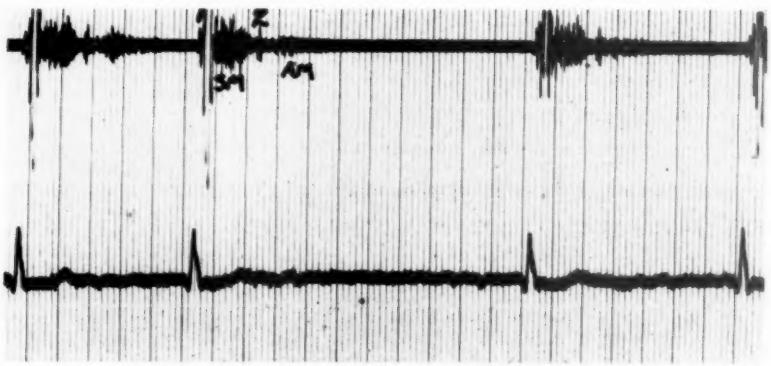

Fig. 5.—Case 2. Same as shown in Fig. 1 but during auricular fibrillation.

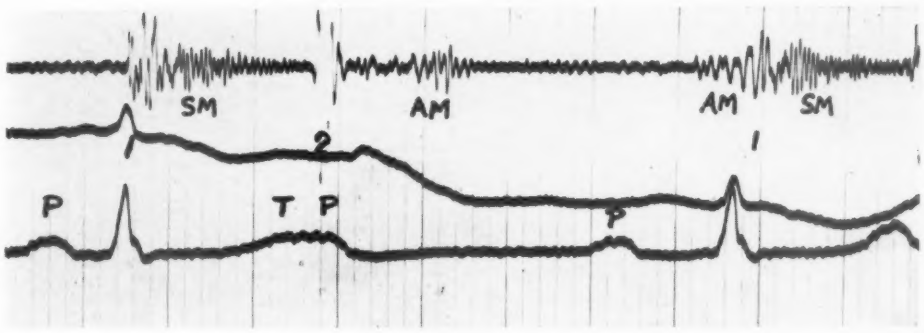

Fig. 6.—Case 3. Same as shown in Fig. 1. Complete A-V block. (Ignore the irregular central tracing.) There is no auricular murmur with the first P wave, P-R interval, 0.20 second, although one is present with a P-R interval of 0.30 second at the end of another diastole of equal length.

The first heart sound varied in intensity. Systole occasionally contained a loud click. At the apex, a short, blowing murmur was heard at variable times in diastole. It was loud during early diastole but became faint by mid-diastole. It was never heard late in diastole, but sometimes double auricular sounds were then noted. This murmur was loudest with the patient recumbent or in the left lateral position, but was also present in the upright position. Very recently the murmur sounded rumbling rather than blowing. It was never heard more than once in any one cycle. Phonocardiograms (Figs. 7 and 8) confirmed these signs, showed their relation to auricular activity, and also revealed a partially split first sound.

Careful radiologic study in 1942 and 1944 failed to demonstrate calcification of the mitral annulus fibrosus. However, in October, 1945, that lesion was shown. The left auricle was then thought to be prominent, although enlargement had not previously been noted. The heart itself was moderately enlarged as in earlier examinations.

Electrocardiograms always showed complete heart block and left axis deviation.

CASE 5.—This man was 40 years of age when he first visited Stanford outpatient clinic in 1923 because of pain which was found to be caused by osteoarthritis. There was no history of rheumatic fever. The heart was normal on physical examination and fluoroscopy. The arterial pressure was 110/80. An electrocardiogram showed only auricular premature beats.

Repeated examinations were negative as late as 1937, when the arterial pressure was 140/90. In 1941 the pressure was 160/100; the heart was regular and not enlarged, and there was a loud systolic murmur over the precordium, loudest along the left sternal border but not reaching the carotid arteries.

In March, 1942, he visited the cardiac clinic because of pain in the chest which was unrelated to effort. The heart rate was 53 and the rhythm was regular. There was a loud apical systolic murmur. During diastole there was also heard at the apex a short, rather low-pitched murmur, which was quite loud in the left lateral recumbent position. There were no signs of congestion. The arterial pressure was 140/80. An electrocardiogram showed sinus bradycardia with prolonged conduction time (P-R interval, 0.51 second) but no other abnormalities. Careful radiologic study including fluoroscopy and roentgenkymograms failed to reveal intracardiac calcification. The heart was not enlarged and the left auricle was not dilated. In 1943 complete heart block was present; the ventricular rate was 36 and the first heart sound varied in intensity. Associated with auricular activity, a blowing but rather low-pitched murmur was heard at the apex in variable phases of ventricular diastole. The murmur was loudest when it came early in diastole.

In 1944, the patient was requested to return for reexamination. He was then 61 years old and was working as a janitor. He appeared to be well and showed no signs of congestive heart failure. The heart rate was 27 and the rhythm was regular. There was a loud, harsh murmur

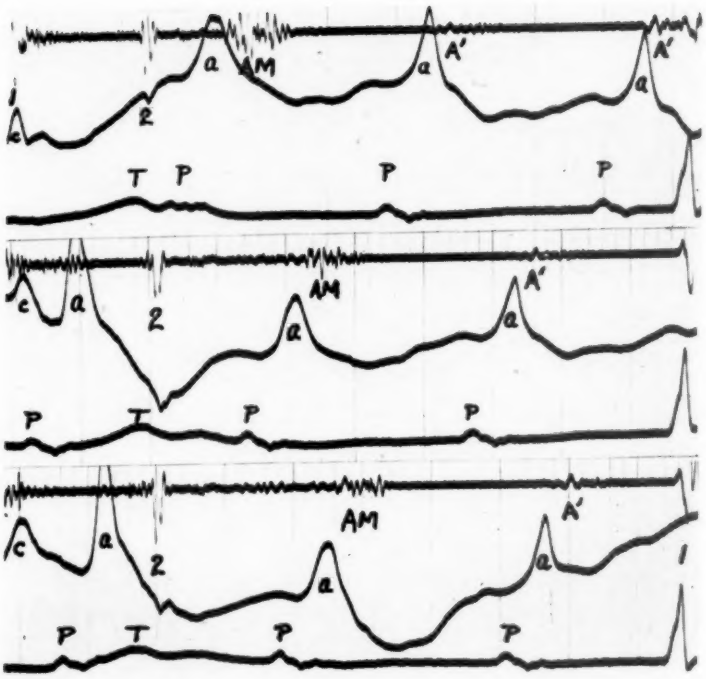

Fig. 7.—Case 4. Simultaneous records of the heart sounds at the apex, jugular pulse, and electrocardiogram. Complete A-V block. Taken from a continuous tracing, each strip represents one ventricular cycle; from above downward, they are first, fourth, and third chronologically. Jugular *a* waves associated with occasionally audible auricular double sound vibrations, *A'*, are no broader or taller than those with auricular murmur, *AM*; *a* waves during ventricular systole are very tall. The auricular murmur follows the *a* wave.

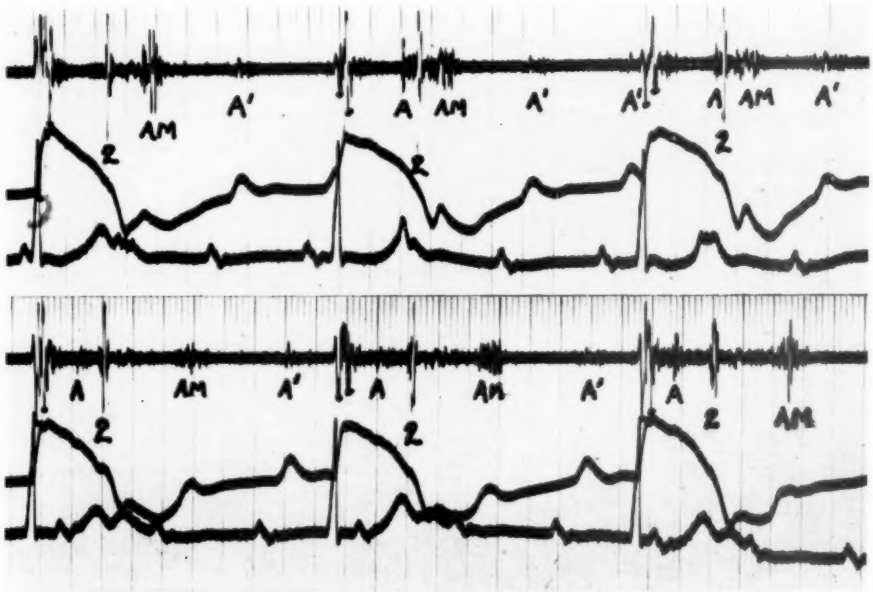

Fig. 8.—Case 4. Simultaneous records of the heart sounds at the apex, apex beat, and electrocardiogram. Complete A-V block. Taken from a continuous tracing, upper and lower strips were separated by two cycles. Dots indicate variable intensities of the partially split first heart sound. In the second and third cycles, a P wave just before the second heart sound is associated with an auricular sound, *A*, in ventricular systole as well as with an auricular murmur, *AM*. The latter follows the second sound by 0.06 to 0.08 second. At times, as in the second cycle, vibrations following the auricular sound during ventricular systole resemble those of a murmur.

at the apex and especially at the left sternal border during ventricular systole. A third heart sound was audible at the apex and was followed immediately by a blowing murmur. Auricular sounds were barely audible late in diastole (Fig. 9). An electrocardiogram showed 2:1 A-V block.

CASE 6.—A man 59 years of age had visited the cardiac clinic for two years because of angina pectoris and dyspnea on effort. He had a history of six attacks of gonococcal urethritis with arthritis, three of them under observation. There was no history of rheumatic fever.

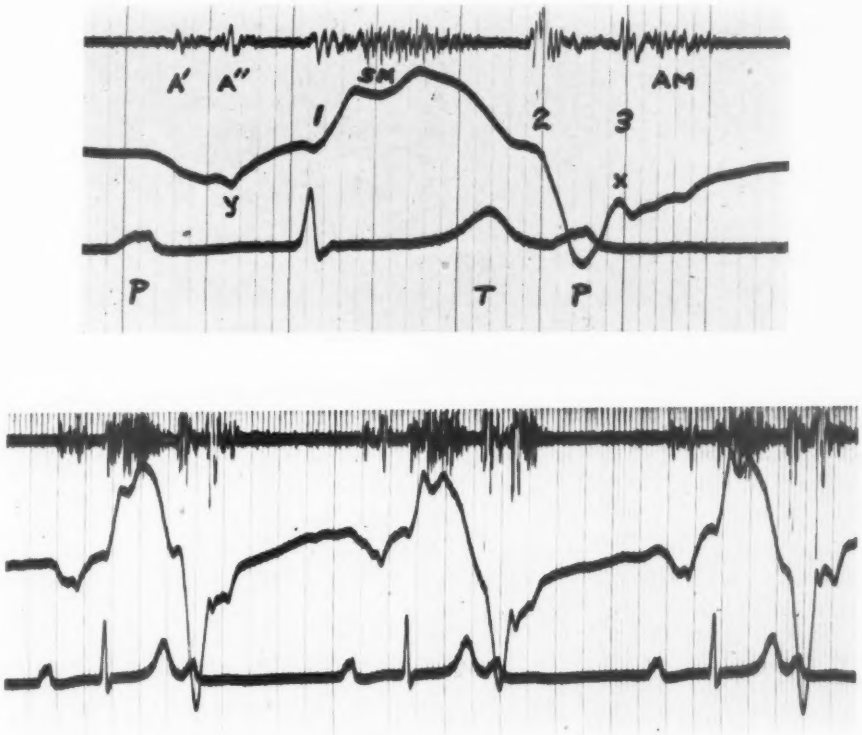

Fig. 9.—Case 5. Simultaneous records of heart sounds at the apex, apex beat, and electrocardiogram. 2:1 A-V block. Upper strip, sensitized paper moving at 75 mm. per second; lower strip, at 25 mm. per second. The first and second components of auricular sounds with the conducted P wave are designated *A'* and *A''*; *AM* is the murmur initiated by the third heart sound, *3*. The latter coincides with the thrust *x* of the apex beat, *A''* with the oppositely directed thrust *y*. With the second and sixth P waves in the lower strip, sound vibrations appear less like those of murmur than like those of double sounds; the second components of these coincide with additional waves in the apex beat.

When the patient was first seen, the heart rate was 60 and the rhythm was regular. No murmurs were noted in the clinic record. The arterial pressure was 180/105. An electrocardiogram showed sinus rhythm with P-R intervals of 0.32 second. When the heart sounds were recorded (Fig. 10) in 1942, there was transient complete heart block but no signs of congestive failure. A faint, blowing apical murmur was noted early in diastole. Radiologic study showed the heart and left auricle to be normal in size. Intracardiac calcification was specifically looked for but was not found.

At the present time he is in the San Francisco Hospital with moderate congestive failure and incomplete heart block. A blowing apical murmur was heard at varying times, especially in early diastole; it was present with the patient in an upright position as well as in a supine; no other signs of mitral stenosis were found.

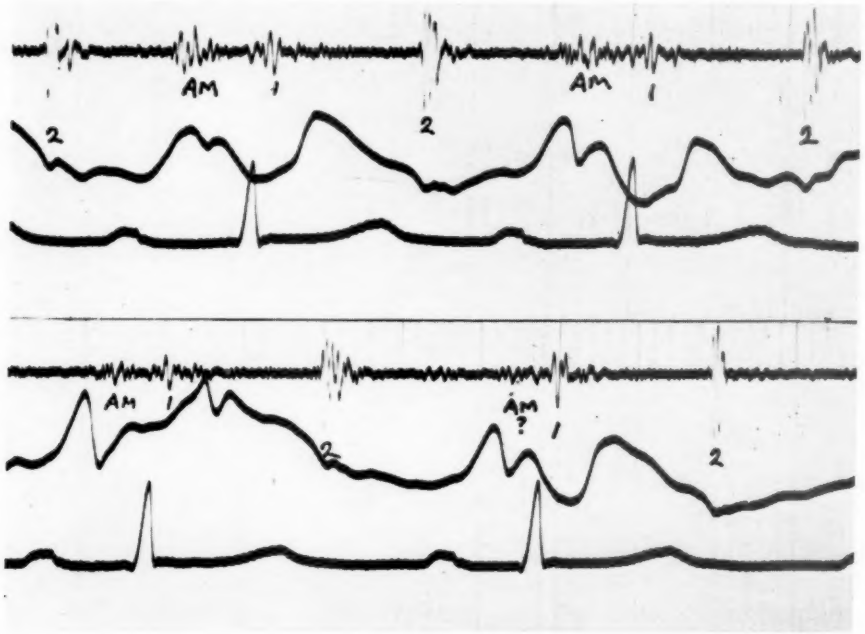

Fig. 10.—Case 6. Simultaneous records of the heart sounds at the apex, jugular pulse, and electrocardiogram. Complete A-V block. Upper and lower strips are consecutive. The auricular murmur, *AM*, was audible when the P wave began 0.16 to 0.18 second after the start of the second heart sound. It was probably inaudible when that interval was 0.22 to 0.28 second. No systolic murmur is recorded.

CASE 7.—A healthy woman 70 years of age consulted a surgeon in 1943 because of ulcers which complicated varicose veins. A murmur was heard in the course of a general examination. There was no history of rheumatic fever.

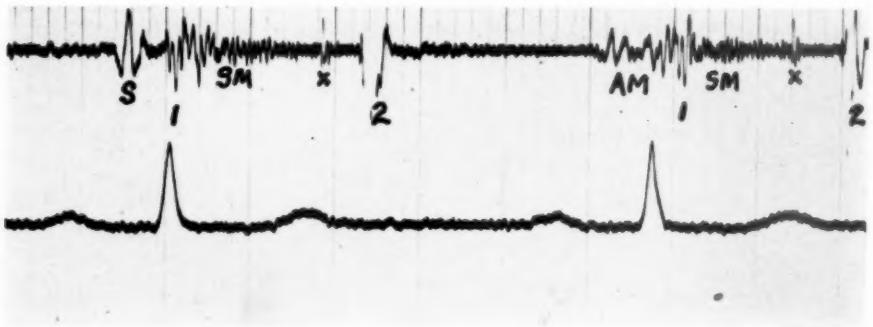

Fig. 11.—Case 7. Simultaneous records of heart sounds at the apex and electrocardiogram. Sinus rhythm, P-R interval, 0.26 second. The usual auricular murmur, *AM*, is occasionally replaced by vibrations of a sound, *S*. There is also an extra sound, *x*, during ventricular systole.

The heart was not enlarged, its rate was 76, and its rhythm was regular. There was a presystolic blowing apical murmur, as well as a loud, rough systolic murmur over the entire precordium (Fig. 11). There were neither signs nor symptoms of congestive failure. Peripheral arteriosclerosis was moderate. Arterial pressure was 200/100. The electrocardiogram revealed only prolonged conduction time (P-R 0.26 second). No calcification could be found within the heart on fluoroscopy or in x-ray films. The heart size was at the upper limits of normal; there was no auricular dilatation.

CASE 8.—A man 53 years of age requested a cardiac examination. He had had chorea repeatedly over three years as a child, and was first told of a murmur when 21 years of age. More recently, hypertension and weakness appeared, and a month before he was seen here there had been an episode resembling pulmonary infarction.

The heart was of normal size, the rhythm was regular, and the rate was 60. There was a blowing presystolic murmur (Fig. 12) and a soft systolic murmur at the apex. The first sound at the apex was split and was not loud. Early diastole was clear. Arterial pressure was 160/100 but fell to 140/85 after a few days in bed. There were no signs or symptoms of congestive failure, and peripheral arteriosclerosis was slight. An electrocardiogram showed prolonged conduction time (P-R interval, 0.32 second) and abnormal T waves, without axis deviation. Careful radiologic study revealed no general cardiac or left auricular enlargement, and no intracardiac calcification.

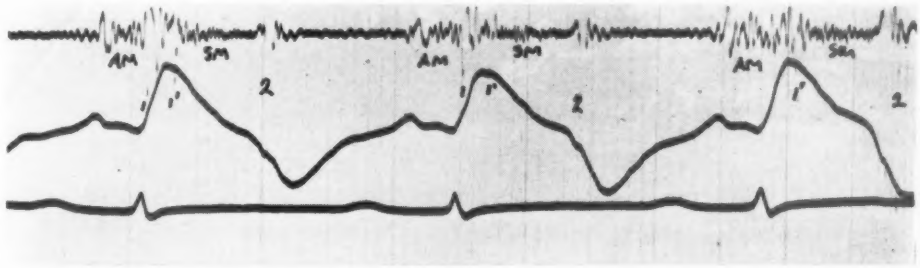

Fig. 12.—Case 8. Simultaneous records of the heart sounds at the apex, apex beat, and electrocardiogram. Sinus rhythm, P-R interval 0.32 second. The auricular murmur, AM, often starts abruptly. The first heart sound is usually split, 1, 1'. The systolic murmur, SM, is inconspicuous.

CASE 9.—A woman 60 years of age gave a history of some sort of rheumatism in childhood. Starting at the age of 24 years, she became progressively more crippled by rheumatoid arthritis. About this time she began to have attacks of paroxysmal tachycardia which became temporarily worse in 1944 when she entered Lane Hospital.

Examination showed extensive rheumatoid arthritis and emaciation but no congestive failure. The arterial pressure was 190/110. There was relatively slight peripheral arteriosclerosis. The heart was moderately enlarged. Its rhythm was disturbed by auricular and ventricular premature beats and by paroxysms of auricular tachycardia. The first heart sound was widely split; there was a loud, blowing murmur between its two elements, best heard at the apex. Diastole was clear; the few presystolic vibrations seen in the sound records (Fig. 13) are probably not a murmur. Electrocardiograms showed P-R intervals of 0.16 to 0.18 second and a wide QRS complex with deep, broad S waves in Lead I. Simultaneous records of the electrocardiogram, heart sounds, and carotid pulse confirmed the presence of right bundle branch block. Radiologic study revealed a moderately enlarged heart but no auricular dilatation or intracardiac calcification.

During an attack of auricular tachycardia, the electrocardiogram showed Wenckebach's periods. Simultaneous records of the heart sounds at the apex (Fig. 13) revealed vibrations of a murmur in the cycles having long P-R intervals and especially in with those with blocked P waves. The murmur was not recognized on auscultation.

A year later an excessive dose of digitalis was followed by an arrhythmia in which the P waves and RS-T complexes were occasionally dissociated, each having a normal rate. When the P wave appeared shortly after the T wave, there was usually a longer-ensuing pause. In these slower cycles, an early short, blowing diastolic murmur was occasionally heard at the apex. This was confirmed at the San Francisco Hospital, but further phonocardiograms could not be obtained. No signs of mitral stenosis were found. The heart was enlarged, and the radiologists believed the left auricle was overly dilated.

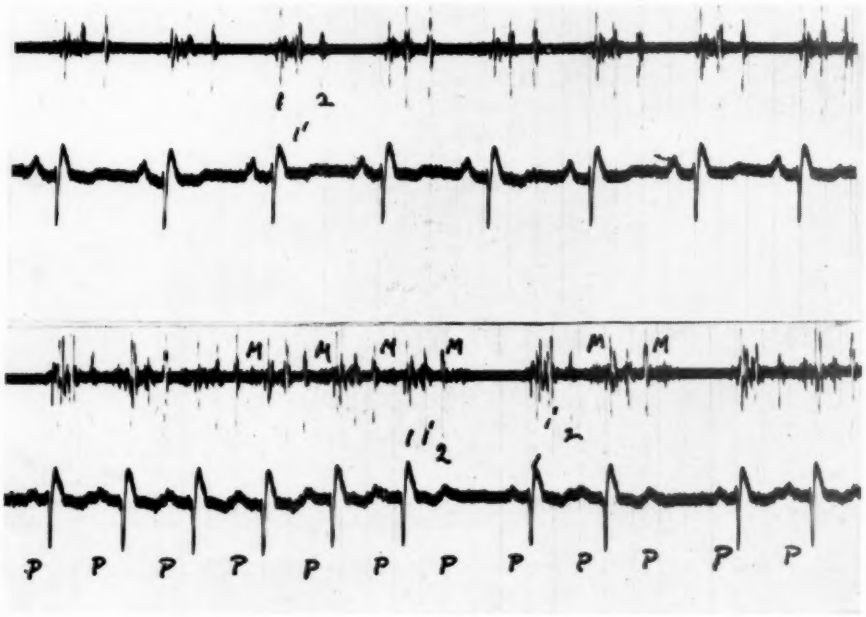

Fig. 13.—Case 9. Heart sounds at the apex and electrocardiogram. Above, sinus rhythm, P-R interval, 0.18 second. The first heart sound is widely split, *1, 1'*, with an unlabeled murmur between the two components and a few presystolic vibrations (not thought to constitute a murmur) before the first component. Below, auricular tachycardia with Wenckebach periods. Vibrations of an auricular murmur, *M*, are visible with lengthening P-R intervals and especially in cycles with complete block.

OBSERVATIONS

A blowing murmur restricted to the apex was clearly heard during ventricular diastole in each of the cases described. Records of the heart sounds in all nine cases showed the vibrations of a murmur, as distinguished from the usual abrupt auricular sounds which occur with heart block, although the latter were occasionally found also. The murmur was louder with the patient in the left lateral recumbent or supine position but could be heard in the upright position except when auricular fibrillation was present. With complete heart block its temporal position varied from cycle to cycle, depending upon the time of auricular activity.

It could then usually be heard twice in each cycle and was always louder when it appeared fairly early in diastole. There was no opening snap of mitral stenosis in any of the patients, and the murmur was never constantly related to the second heart sound except as noted later in the paper.

The following measurements were made on simultaneous records of the heart sounds and an electrocardiographic lead, avoiding parallax; in some cases cardiovascular pulsations were also recorded. It is recognized that these data are not as accurate as could be desired because of such difficulties as locating the earliest vibrations of the murmur. Nevertheless, some of the findings seem significant.

Interval from P Wave to Murmur.—The interval between the onset of the P wave of the electrocardiogram and the onset of the murmur averaged 0.15 to 0.16, 0.16, 0.23, 0.18, 0.14 to 0.16, 0.17, 0.16, and 0.18 second in Cases 1 through 8, respectively.

Interval From Second Heart Sound to Murmur.—Except under special conditions, there was no murmur related by a definite time interval to the second heart sound. In Case 1 a murmur was often recorded with onset about 0.12 second after the second sound whenever a P wave began just before that sound (Fig. 1). The amplitude of these vibrations was less than when the murmur appeared later in diastole. In Case 4, the second heart sound often preceded a murmur by 0.06 to 0.08 second whenever the P wave fell comparatively late in ventricular systole (Fig. 8).

With auricular fibrillation in Cases 1 and 2, a faint apical murmur was found in early diastole (Figs. 2 and 5). It started about 0.19 second after the second heart sound in Case 1, 0.12 second or less in Case 2.

Auricular Sounds.—In some of the patients phonocardiograms at times revealed abrupt auricular sounds, as distinguished from murmurs.

In Case 1, vibrations incorporated within the auricular murmur resembled those of a sound when the murmur began, roughly, 0.3 to 0.6 second after the second heart sound. These vibrations occurred about 0.21 second after the start of the P wave.

In Case 4, the murmur was only heard very early in ventricular diastole. Phonocardiograms (Fig. 7) show that its vibrations became small rather suddenly, in different cycles, whenever the P wave began later than about 0.5 second after the last second heart sound. With P waves later than that, there were a few small, slow vibrations starting 0.20 second after the onset of the P wave. These did not differ appreciably whether their associated P wave began 0.6 or 1.3 second after the last second heart sound. They were sometimes identified on auscultation as faint, double auricular sounds but were usually inaudible. In this patient, in whom the murmur of ventricular systole was short and faint at the apex, a loud clicking auricular sound was occasionally heard and recorded before the second heart sound. Late in ventricular systole such sounds started 0.10 second after the P wave, while earlier in systole the interval was about 0.14 second. The recorded appearance of the sound varied (Fig. 8) and occasionally even resembled that of a murmur.

In Case 5, with 2:1 block, auricular sounds were associated with both blocked and conducted (P-R interval, 0.45 second) P waves. With the latter, double auricular sounds (faintly audible but not separated on auscultation) were recorded. The first component occurred 0.14 second and the second component 0.28 second after the onset of the P wave. The blocked P wave, which started 0.06 second after the second heart sound, was followed 0.16 second after its onset by a loud third heart sound which was noted clinically and initiated the auricular murmur. On the other hand, records occasionally showed vibrations which looked like a murmur with the conducted cycle. Finally, the usual murmur following the third sound was sometimes absent. In this event there was usually a fourth sound, 0.16 second after the third and associated with a downward deflection of the apex beat curve (Fig. 9). In this patient, records made during complete block showed only a murmur, starting 0.14 to 0.16 second after the P wave.

In Case 7, especially with the patient in the left lateral recumbent position, the murmur was sometimes initiated or replaced by a recorded vibration which had the appearance of a sound (Fig. 11). A mid-systolic click was also noted.

Apex Beat.—In Case 5, a sharp upward deflection of the apex beat curve accompanied the third sound, which followed the onset of the blocked P wave by 0.16 second and which was at once followed by the auricular murmur (see also preceding section). In the same patient, the second component of the auricular sound with conducted P wave was associated in the apex beat with a sharp downward deflection 0.28 second after the onset of the P wave, followed at once by a slow rise (Fig. 9).

A similar slow, small rise in the apex beat curve began 0.16 to 0.24 second after the onset of the P wave in Case 2 and 0.16 second in Cases 3 and 8. The significance of this rise is not clear, but it is not thought to represent auricular systole.

In Case 4 (Fig. 8) a larger upward movement of the recorded apex beat began 0.14 second and reached its peak 0.22 second after the onset of the P wave. It did not occur with P waves during ventricular systole and its appearance and timing did not vary with the location in ventricular diastole, a finding which may be related to the following observation.

Jugular a Wave.—The behavior of the jugular *a* wave was especially noteworthy in Case 4. When the *a* wave occurred late in ventricular diastole without an audible murmur, its amplitude was no greater than that of an *a* wave associated with a murmur early in diastole. The same records show markedly increased amplitude of *a* waves during ventricular cystole, as expected (Fig. 7). Judging by this observation, ventricular filling even for 1.3 seconds after the last second heart sound (and further aided by two intervening auricular systoles) does not impede outflow from an auricular contraction occurring late in ventricular diastole.

In Cases 2 and 4, the murmur began at or after the peak of the *a* wave, a point which was also associated with the first component of the double auricular sound in Case 5.

The jugular *a* wave began 0.08, 0.10, 0.10, and 0.09 second after the onset of the P wave in Cases 2, 4, 5, and 6, respectively. Since these findings are in the normal range, they indicate no delay in right-sided auricular systole.

DISCUSSION

Mitral Stenosis.—An apical murmur related to auricular activity is at once suggestive of mitral stenosis, but that lesion did not appear to be present. Calcification of the mitral annulus fibrosus, such as found in Cases 1 through 4, might be expected to obstruct flow through that orifice but actually does so only rarely; in five other patients with calcification but with P-R intervals of 0.14 to 0.18 second this murmur could not be heard or recorded.[1]

No patient had the other physical signs of mitral stenosis; namely, loud or split pulmonic second sound, loud first heart sound (except when accentuated in cycles with short P-R intervals), opening snap, or early diastolic murmur constantly related to the second sound (in the absence of auricular fibrillation). Right axis deviation was never present, nor was the P wave abnormally large. The left auricle was not often prominent, except with general cardiac enlargement or auricular fibrillation. Although the auricular murmur was enhanced in the left lateral recumbent position, it was usually blowing in quality, quite unlike the rumble of rheumatic mitral stenosis; in Case 2 it was rather rough, and in Case 4 became rumbling after several years.

Aortic regurgitation was not present, so the Austin Flint murmur need not be considered. An auriculo-systolic murmur which has been heard at the tricuspid area during convalescence from myocardial infarction[2] is likewise unrelated to the present discussion.

A murmur suggestive of mitral stenosis has been found in patients without that lesion but with anemia[3,4] or congestive heart failure[5,6] and is usually attributed to stenosis relative to dilated cardiac chambers. While congestive failure was sometimes present, it was never more than mild when the foregoing observations were made in these ambulatory patients, of whom none was anemic. Heart block itself produces cardiac dilatation but has never been thought to cause a murmur. Stenosis of the mitral orifice relative to such distention should give a murmur louder in later diastole, whereas the opposite was true.

One of the main reasons for rejecting mitral stenosis, actual or relative, as the cause of the murmur is the latter's delayed onset after the P wave. Probably because of the difficulties in locating accurately the onset of a murmur in records of the heart sounds, there are but few data to indicate the temporal relationships of the presystolic murmur in rheumatic mitral stenosis. Calculations based on the observations of Lewis[7] and Bramwell[8] suggest that such a murmur starts 0.03 to 0.15 second after the beginning of the P wave, with which a few records in this laboratory agree. In the present patients the murmur began 0.14 to 0.23 second after the P wave. Their jugular *a* waves revealed no delay in the onset of right auricular contraction, and there is no reason to believe that systole of the left auricle did not coincide with that of the right. Furthermore, it was

possible to find cycles with normal P-R intervals in the patients with complete heart block. At such times vibrations of a murmur were not visible in the phonocardiograms (Figs. 1 and 6).

Temporarily ignoring its presence early in diastole with auricular fibrillation, the murmur appears to be an event which *follows* auricular contraction. The evidence given seems to indicate that it is neither caused by obstruction to flow nor coincident with auricular systole.

Mitral Insufficiency.—It is conceivable that the apical murmur which follows after auricular systole during ventricular diastole is the result of regurgitation of blood back into the auricle, with mitral insufficiency.

If this were the case, a murmur might also be expected to occur at the close of the period of early diastolic rapid filling. This did occur faintly in Cases 1 and 2 during auricular fibrillation, but only then. Regurgitation perhaps should also increase, presumably with a louder murmur, when the ventricles are more full late in diastole. Observations showed the opposite.

Mitral insufficiency as a cause of the murmur would be supported by its demonstration during ventricular systole. With the slow rate of heart block and with arterial hypertension, circulatory conditions were optimal for regurgitation of blood if mitral insufficiency were actually present.[9] A systolic murmur was frequently heard at the apex, and in a general way its intensity was paralleled by that of the auricular diastolic murmur. However, it was usually fainter at the apex than along the left sternal border, was once confined to the interval between the widely split components of the first heart sound, and was not conspicuous in every case. It might have been produced by aortic dilatation with arteriosclerosis.

It is generally held, though perhaps incorrectly, that mitral regurgitation may be present without radiologic evidence of left auricular dilatation or abnormal pulsation of that chamber in roentgenkymograms. At any rate, the left auricle was not prominent in any of the patients during the period in which most of the observations were made. It did, however, enlarge somewhat later on in Cases 2, 9, and perhaps 4. This might have been the result of auricular fibrillation and progressive congestive failure. Study of the roentgenkymograms in Cases 1, 2, 4, 5, and 6 showed none of the findings thought to be typical of mitral regurgitation.[10]

In brief, regurgitation through the mitral leaflets at the close of auricular systole may be a simple explanation for the murmur, but there is little evidence to substantiate its occurrence. The frequent association of the murmur with auricular sounds and its occasional replacement by them are adequate reasons for consideration of other possible mechanisms.

Relation to Heart Block.—The murmur occurred only in patients with heart block. Auricular activity during that arrhythmia ordinarily results in abrupt sounds, not murmurs. At times, phonocardiograms of this event have revealed prolonged vibrations[11] which do not appear to have been clinically interpreted as murmurs.

Wolferth and Margolies[12] and Stead and Kunkel[13] reported two cases of heart block, each with an audible murmur similar to that now being discussed. The causes of block were not altogether clear. There were no other signs of mitral stenosis, and the patients were aged 49 and 57 years. The murmur started 0.14 to 0.16 second after the onset of the P wave. Apparently the murmur was not present in Case 1 of Wolferth and Margolies' series during periods of sinus rhythm with normal P-R intervals. A presystolic murmur was heard and recorded in the case of Stead and Kunkel with the P-R interval as short as 0.20 second (during 2:1 block) and was noted during sinus rhythm with which the P-R interval was never found to be less than 0.22 second.[14] These two cases and the nine reported here seem to be the only recorded instances of audible auricular murmurs in heart block (without obvious mitral stenosis). Such a murmur will surely be found more often in elderly patients with defective auriculoventricular conduction, once the possibility of its occurrence is appreciated.

Limitation of the murmur to patients with heart block must be the result simply of delayed ventricular contraction, permitting an adequate interval of time to elapse after the conclusion of auricular systole; the conditions productive of the sounds or murmurs which may be heard in this interval would otherwise be prevented.

Heart Sounds During Ventricular Filling.—Since the murmur began 0.14 to 0.23 second after the start of the P wave, or about 0.12 to 0.19 second after the second sound in the presence of auricular fibrillation, it becomes pertinent to inquire into what is known of cardiodynamics and sounds during those periods.

Early in diastole, ventricular filling commences abruptly at the time indicated by the position of the opening snap of mitral stenosis, 0.07 to 0.13 second after the second heart sound.[15] This phase of rapid filling comes to an end 0.12 to 0.20 second after the second sound. Here a normal third heart sound or an early diastolic gallop may be present[15] and this is the range of time in which the murmur began in Cases 1 and 2 in the presence of auricular fibrillation.

In both laboratory animals and man,[16] auricular systole appears to begin about 0.03 to 0.04 second, and the jugular *a* wave about 0.08 to 0.10 second, after the start of the P wave. In at least four of the present patients jugular *a* waves indicated no delay in the onset of mechanical systole of the right auricle. The duration of increased intra-auricular pressure may be 0.13 to 0.15 second.[17,18] Therefore, the phase in which ventricular filling is accelerated by auricular systole is at an end some 0.16 to 0.19 second from the start of the P wave. This, roughly, is in the time range of the onset of the murmur now under discussion. It is also near the time at which another sound may be recorded; while a presystolic gallop is often found 0.08 to 0.14 second after the beginning of the P wave, this interval lengthens in ambulatory patients with milder congestive failure to 0.12 to 0.17 second.[19]

Some of the auricular sounds found in heart block follow the P wave by an even greater interval. Omitting a preliminary sound recorded only from the auricular wall or through the esophagus, two groups of workers[11,20] place the first

component of audible auricular sounds at 0.06 to 0.08 or 0.12 second and the second component at 0.17 to 0.24 or 0.20 to 0.24 second from the start of the P wave. Our findings are in better agreement with Wolferth and Margolies,[15] who give intervals of 0.08 to 0.14 and 0.24 to 0.30 second, respectively, for the two components. We also agree with the latter observers that it is only the first component which is recorded during ventricular systole.

At least part of the variations and discrepancies in the foregoing data may result from differences in age, degree of heart failure, presence of valvular or other lesions, etc., in the patients studied; it might be more helpful if future writers on heart sounds considered some of these factors. Clarification of the present uncertainties as to the causes of diastolic sounds would obviously be greatly desirable.

Based in part on Dean's[21] experiment, Lewis and Dock[22,30] suggested that the third heart sound and gallop sounds may occur at the end of rapid-filling phases if the auriculoventricular valve leaflets are then closed or drawn taut. Not all workers agree with this view.[15] Dean,[21] using the excised heart of the cat, found that the mitral cusps swing up and are momentarily approximated at about 0.15 second after the start of mechanical auricular systole. The cusps separate again 0.12 second later. These times come 0.18 and 0.30 second after the onset of the P wave, and the first is compatible with the start of the murmur; for comparison with Dean's time of valvular separation, the final vibrations of the murmur occurred about 0.31 to 0.37 second after the onset of the P wave in Cases 1 through 6. There is, of course, an obvious risk in comparing events in excised cat hearts and abnormal human hearts.

The data presented in this section are consistent with the view that the murmur in these elderly patients starts near the end of phases of accelerated ventricular filling, at times when short sounds may be heard in other subjects. Such sounds, in fact, occurred in the present patients occasionally, either replacing the murmur or associated with it. The temporal relationships of the murmur are similar to those of a period during which experimental studies have demonstrated the approximation of mitral leaflets following auricular systole. Approximation was not found after the early diastolic phase of rapid filling,[21] nor did the murmur occur then except twice; on both occasions auricular fibrillation was present and the murmur was much fainter.

It seems very likely that the murmur is produced by some mechanism which does not interfere with the movements of the valve leaflets during periods of rapid flow but which modifies their presumably more delicate aftermovements.

Aging of the Valve Leaflets.—This sort of mechanism might have an anatomic explanation in the increased thickness and rigidity of valve leaflets known to occur with advancing years, especially on the left side of the heart.[23-25] There seems to be no direct information regarding the effect of aging on the mobility of leaflets, but some indirect data may have a bearing.

Wolferth and Margolies[12] found, in two young patients with heart block, two zones of intensification of the first heart sound; the first was with P-R in-

tervals of less than 0.14 to 0.20 second, the second with P-R intervals greater than 0.32 second. In three older patients the second zone was not present. These findings have been confirmed by unpublished observations in this laboratory. Expressing the results differently, the first heart sound is relatively faint in children when the P-R interval is between 0.14 to 0.20 and 0.32 second, the time of the murmur in our patients and that of approximated mitral leaflets in Dean's[21] experiment. It is faint in elderly patients at all times after P-R intervals of 0.14 to 0.20 second.

The explanation of the variable intensity of the first heart sound in block is not entirely clear, but the hypothesis that accentuation takes place whenever "systole occurs at an instant when inflow from the auricle is pushing the valves toward the apex and separating the leaflets as much as possible"[22] is attractive and appeals to others.[13] The corollary is a faint first heart sound whenever the leaflets are approximated at the onset of ventricular cystole. According to this view, the mitral leaflets of children swing apart again some 0.32 second after the P wave, while those of older subjects do not.

The forces concerned with the play of the cardiac valves during ventricular diastole are not definitely known[26] but may involve eddy currents or "the lateral inrush into the wake of the breaking jet just beyond the ostium."[27] An inrolling type of motion of pliable young leaflets with the force of lateral inrush is thought to close the valve without regurgitation; rigid old leaflets, swinging like a door on hinges, may permit regurgitation.[27] Furthermore, the leaflets of the elderly are said to be "less nicely approximated"[23] than in youth, again suggesting regurgitation as the cause of the murmur.

On the other hand, these forces may be sufficient to narrow the mitral orifice while blood is flowing through in a forward direction,[18,26] apparently even with thin normal leaflets. If this is so, it is conceivable that the murmur is produced by the more prolonged apposition of thick, rigid cusps under similar conditions, perhaps with vibration of the leaflets.

Since valvular aging appears to begin in the second or third decades, this may be at least a partial explanation for the decreasing frequency of the normal third heart sound with age. Leaflets becoming less pliable might fail at normal pressures to behave in the manner thought to produce the third sound[22] but could again respond to the increased intra-auricular pressure of heart failure with a gallop sound.

The Murmur in Relation to Phase of Ventricular Diastole.—In general, records of the heart sounds revealed that the greatest amplitude of the murmur's vibrations was found when the murmur began near the end of the early diastolic rapid-filling phase (Figs. 1, 3, 6, 7, 8, and 10). The vibrations were usually smaller after this period, except for a few of large amplitude, as if a sound were bracketed by the murmur. They were certainly smaller before this period. This fact may be less significant because the associated P wave often started in or near the end of ventricular systole.

Other observers [8,12,13] have also noted the diminishing intensity of auricular murmurs in heart block as auricular activity comes later in ventricular diastole. Their logical explanation is that during diastole the filling ventricle becomes less able to receive blood with later or successive auricular contractions. This seems so obvious that it came as a surprise to find both old[28] and new[18] experiments which suggest that this need not be so.

In Case 4 the behavior of the jugular *a* wave failed to reveal right ventricular inability to receive blood late in diastole. Its amplitude and duration were no greater when it occurred more than 0.5 second after the second sound, without an audible murmur, than when it occurred less than 0.5 second after the second sound and with a murmur (Fig. 7). With the closed valve of ventricular systole, the *a* wave was tall, as expected. In fact, the tracing seems to show broader and less peaked *a* waves *early* in diastole, especially with the earliest and greatest murmurs. If this is significant at all, it is in the direction of supporting the concept of greater resistance to auricular systolic ejection when this comes with the early rapid-filling phase.[18]

In other patients the murmur occurred at any time in diastole, starting as late as 0.8, 0.9, and 1.1 seconds following the last second heart sound in Cases 1, 3, and 5, even though the auricles had contracted once before in those cycles. Closer inspection of Fig. 11 for Case 1 of Wolferth and Margolies' series[12] lends further support to the conception that the murmur's amplitude is not so much decreased in late diastole as it is increased when approaching the zone of the third heart sound. The latter was pointed out in their legend.

When the P-R interval of the final P wave in a ventricular diastole was 0.20 second or less, no vibrations of a murmur were recognizable. With P-R intervals just a few hundredths of a second longer, vibrations were readily apparent (Figs. 1 and 6). Such a short difference of time cannot well explain the absence of the murmur by further ventricular filling in that interval but must be taken as confirmation of a relatively late onset of the murmur after the P wave. This is analagous to the absence of a murmur in elderly patients with normal conduction times.

Incidentally, the first heart sound was accentuated in Cases 1, 3, 4, and 5 with short P-R intervals, but not when the P-R interval was long enough, 0.20 second or more, to permit recognition of a murmur's vibrations. This probably means the mitral leaflets were no longer widely separated by auricular systole when the murmur was produced, in further agreement with its delayed onset.

The early, rapid-filling phase failed to provoke any but a faint murmur which occurred twice and only with auricular fibrillation. Even auricular systole was not always followed by the murmur, especially after a long diastole. Apparently the two events are more powerful when in conjunction, in which connection it is interesting that Cossio[29] found a third sound with heart block when the P wave fell immediately after the T wave of the preceding cycle in patients who otherwise had neither auricular sounds nor third heart sounds.

As an alternative to mitral regurgitation, the following hypothesis is proposed. After auricular systole, normal mitral leaflets are floated nearly together. In

the aged, they remain longer and more fixed in that position because of their increased rigidity. The murmur occurs then with continuing forward flow through the relatively narrow orifice. It is loudest in the part of early diastole which follows the phase of rapid filling because the valvular play after this event reinforces the valvular play after auricular systole and because the blood flow is still great. When the murmur disappears or is replaced by the usual short auricular sounds in late diastole, it is because the flow has become slow. This is more the result of moving away from the early phase of rapid filling than of ventricular inability to receive blood. The lesion is not adequate to hamper flow during the rapid ejection phases themselves.

SUMMARY AND CONCLUSIONS

Observations are reported on a blowing apical murmur related to auricular activity in nine elderly patients with heart block. At times the murmur was associated with, or replaced by, short auricular sounds.

There was no convicing evidence of rheumatic mitral stenosis. Calcification of the mitral annulus fibrosus was demonstrated in four cases. Other patients with this lesion but without conduction defects do not have such a murmur.

The onset of the murmur seemed to occur just after the end of auricular systole. In the presence of auricular fibrillation, it began near the end of the rapid-filling phase of early diastole. These are the times at which gallop sounds may be present in other patients.

In the absence of auricular fibrillation, there was no murmur in relation to the second heart sound unless auricular activity happened to take place at that time.

The murmur was loudest when auricular activity more or less coincided with the end of the early rapid-filling phase. Both earlier and later in diastole, the murmur was fainter.

An explanation other than inability of the filled ventricle to receive blood late in diastole is offered to account for the diminished intensity of the murmur at that period.

Mechanisms which might be responsible for the production of the murmur are discussed in relation to current conceptions of cardiodynamics and heart sounds during ventricular diastole.

Reasons are given for believing that the murmur may be caused by modifications of the movements of the mitral valve leaflets at the end of periods of accelerated ventricular filling, especially after auricular systole.

The lesion responsible for such a mechanism may be the result of aging of the leaflets, without interference to flow during rapid ejection phases.

It is further suggested that aging of the leaflets could account for the disappearance of the normal third heart sound and its return as a gallop during heart failure.

This is another murmur which may be heard at the cardiac apex during diastole in the absence of mitral stenosis.

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HYPERTROPHY OF THE HEART OF UNKNOWN ETIOLOGY IN YOUNG ADULTS: REPORT OF FOUR CASES WITH AUTOPSIES

COMMANDER ROBERT F. NORRIS, M.C., AND LIEUTENANT COMMANDER HARRY H. POTE, M.C., UNITED STATES NAVAL RESERVE

IN ONE year at the Philadelphia Naval Hospital, four men between the ages of 21 and 30 years, with histories of progressive congestive failure, died of unexplained hypertrophy and dilatation of the heart. Neither clinically nor at autopsy was the etiology of the hypertrophy determined. All of them had been under repeated medical observation for at least two years and at no time, even before the onset of cardiac symptoms, was there any evidence of hypertension or of other factors which commonly result in hypertrophy of the heart. At autopsy, there was no valvular disease and the large and small coronary arteries were considered normal for this age. Hypertrophy of individual muscle fibers was the most conspicuous microscopic abnormality. There was evidence of focal degeneration of the myocardium, but the lesions were not so extensive as to constitute a diffuse myocarditis.

Although cases of unexplained sudden death presumably of cardiac origin during this period of life are occasionally seen at autopsy, particularly by coroner's physicians, hypertrophy of the heart in the absence of anatomic defects is usually not pronounced. In the present cases, however, death, although at first unexpected, was not sudden except in one patient (Case 2), occurred only after progressive congestive failure, and was associated with distinct hypertrophy of the heart. In older patients, clinically unexplained congestive failure and hypertrophy of the heart are usually ascribed to a previously unrecognized hypertension or to arteriosclerosis of the smaller coronary arteries and arterioles. In none of the cases to be described was there any evidence of either of these factors.

In 1933, Levy and Rousselot[1] reported three cases of similar age which resemble ours, but found only two others[2,3] in the literature. In 1937 Levy and Von Glahn[4] reported eight cases from 29 to 66 years of age. Since that time, we have found no further reports. In view of the rarity of unexplained hypertrophy of the heart in the third decade, therefore, a report of four such cases is justified.

Now at the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania, Philadelphia, Pa.

The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

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REPORT OF CASES

CASE 1.—

Clinical History.—J. U., a white man, aged 28 years, was admitted to the Philadelphia Naval Hospital on Aug. 9, 1944, complaining of shortness of breath and swelling of ankles of about three weeks' duration. The family and past medical histories were irrelevant. He enlisted in the United States Coast Guard on April 19, 1940, and had no overseas duty. He was apparently well until Nov. 17, 1942. At this time an appendectomy with drainage was performed for gangrenous appendicitis. He had no further abdominal complications and the incision healed satisfactorily. On the fourth postoperative day, he had fever and cough and was thought to have pneumonia, but this was not confirmed since no x-ray examination of the chest was made. These symptoms subsided in a few days, however, without the administration of sulfonamides. An x-ray film of the chest on the twelfth postoperative day showed no evidence of pneumonia but did show the heart to be symmetrically enlarged. Without further study, he was discharged to duty on Dec. 12, 1942, the eighteenth postoperative day. On Jan. 4, 1943, because of exertional precordial pain and palpitation of three days' duration, he was readmitted to a hospital. Except for an enlarged heart, no significant findings were reported on physical examination. He was discharged from the service because of heart disease on Feb. 12, 1943. The highest blood pressure was 120/90. He was always afebrile.

Following discharge he was asymptomatic and was able to work as a packer for nearly eighteen months. During this period he was examined frequently at a Veterans' Administration facility, but no further abnormalities were discovered. On July 18, 1944, however, he noticed shortness of breath and on the advice of a family physician he stopped work. The dyspnea persisted, even while at rest, and on August 9, he coughed up blood-tinged sputum and noticed that his ankles were swollen. He was admitted for the first time to this hospital on the same day.

On admission he was cyanotic and orthopneic. The legs were markedly edematous. The heart was greatly enlarged, the rhythm was regular, and the heart rate was 124 per minute. There were no murmurs. Blood pressure was 100 systolic, but the diastolic was not determined. Numerous râles were heard over the lungs and the liver was enlarged three fingerbreadths below the right costal margin. He grew progressively worse and died on Sept. 11, 1944, thirty-three days after admission.

Laboratory Data.—During hospitalization for appendectomy, no electrocardiogram was made. On the second admission, an electrocardiogram was reported as normal. On final admission, an electrocardiogram before digitalis was given showed left-axis deviation, QRS interval of 0.16 second, indicating bundle-branch block, elevation of RS-T segment in Leads II and III and depression in Lead CF_4, and inversion of T waves in Lead I (Fig. 1). At the time of the appendectomy, there was a transient leucocytosis, and shortly before death the white blood count was 33,000, of which 91 per cent were polymorphonuclear neutrophiles. A sedimentation rate was not determined at this time but was previously normal. Other laboratory data, including urinalysis, red blood cell count, hemoglobin, blood Kahn, and blood urea nitrogen were within normal limits.

Autopsy (No. 44-182).—

Anatomical Diagnosis: There were hypertrophy and slight focal scarring of myocardium; marked dilatation of all chambers of heart; chronic passive congestion of the lungs and liver; lobular pneumonia; slight atherosclerosis of the aorta; former operative removal of the appendix; and an operative scar in the right lower quadrant of abdomen.

Body: The body and the individual organs grossly and microscopically showed extensive chronic passive congestion, but there were no other relevant lesions except for terminal pneumonia.

*Heart:** The heart weighed 890 grams. The myocardium of both ventricles was hypertrophied but there were no focal lesions. Both auricles and ventricles were greatly dilated. Although the valves were all thin and delicate, the endocardium of the left auricle was opaque and

*Since the hearts of all cases grossly showed only hypertrophy and dilatation, photographs are not included.

slightly but diffusely thickened. The coronary arteries were patent. Only very small atheromatous patches were present in their intima.

Microscopically in numerous sections, including both ventricles, both auricles, and the mitral and aortic valves, there were no areas of inflammation. The muscle fibers of the left ventricle were diffusely hypertrophied and those of the left auricle and ventricle were also increased in thickness. Minute areas of stellate scarring were present in the left ventricle but not elsewhere in the myocardium. The small branches of the coronary arteries were normal.

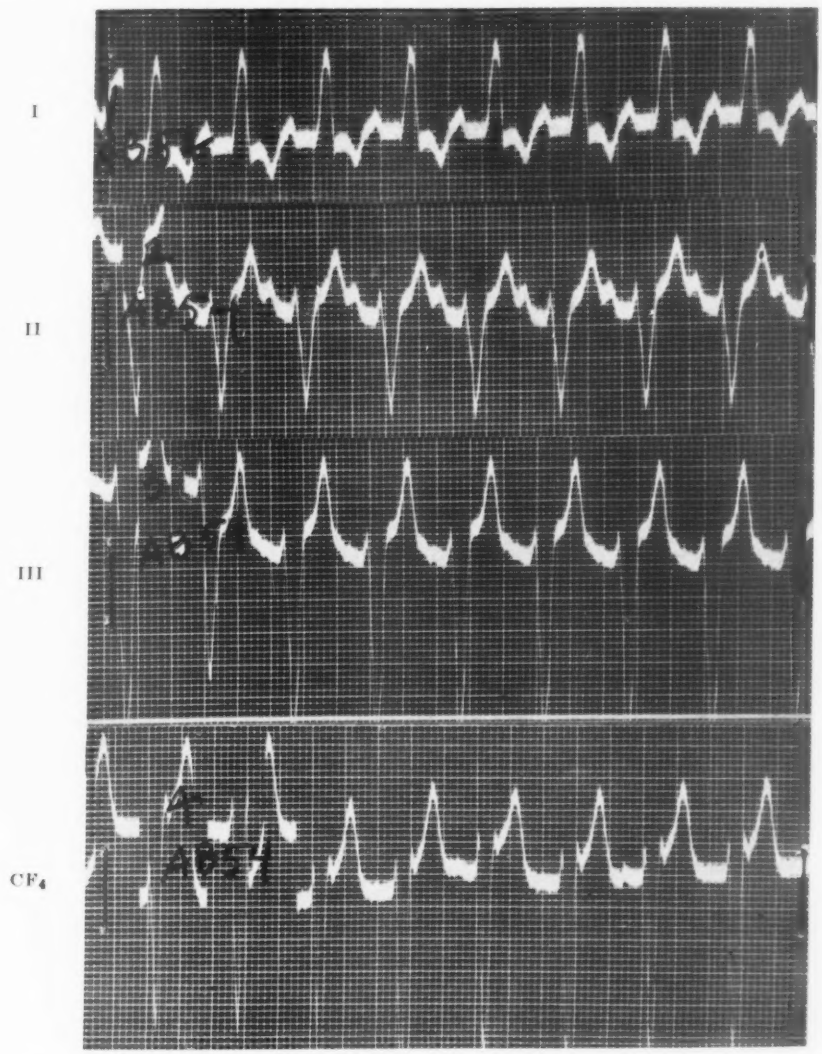

Fig. 1.—Case 1.—There are left-axis deviations; QRS interval of 0.16 second; elevation of RS-T segment in Leads II and III and depression in Lead IV; and inversion of T waves in Lead I; probable bundle-branch block.

CASE 2.—

Clinical History.—E. P. M., a white man, aged 21 years, was admitted to the Philadelphia Naval Hospital on Aug. 22, 1944, complaining of severe pain in the chest of a few hours' duration. The family and past medical histories were irrelevant. He enlisted in the United States Army some time prior to July, 1942. He had no overseas duty. He was apparently well until some time in June, 1943, when he had a "cold" which was followed by cough, weakness, and dyspnea on exertion. The cough subsided but the weakness and dyspnea continued and he began to lose weight. He was first admitted to the sick list because of these symptoms on July 14, 1943. At that time, the only abnormalities, on physical examination, were pallor and small blood clots in the nasopharynx. He was found to have a severe anemia which was considered to be hypochromic and either microcytic or normocytic Following one transfusion with whole blood and treatment with liver extract, iron, and multiple vitamins, the blood count rapidly returned to normal and he was discharged to duty on Sept. 3, 1943. He was well until about the middle of December of the same year, when the symptoms of weakness and susceptibility to fatigue returned and persisted until the time of his second admission on Jan. 5, 1944. He had lost about fifteen pounds since his discharge and again was pale and anemic. Treatment with whole blood transfusions, liver extract, iron, and multiple vitamins was again effective, but whenever this regimen was discontinued the anemia recurred. At this time an x-ray film of the chest showed a normal cardiothoracic ratio, but the heart appeared to have enlarged when compared with the cardiac silhouette of July, 1943. Since there was also electrocardiographic evidence of myocardial change, he was discharged from the service on April 8, 1944. At this time he had a normal blood count and was asymptomatic. During the periods of hospitalization, the blood pressure was never above 110/85. He was always afebrile.

Following his discharge he had worked regularly and remained well until Aug. 22, 1944, when he was admitted to this hospital because of sudden, severe, persistent precordial pain.

On admission he was cyanotic and orthopneic. The ankles were moderately edematous; the heart was moderately enlarged, the rhythm was regular, the rate was 112, and a soft systolic murmur was localized at the apex. The blood pressure was 110/85. Many râles were heard over both lungs, and the liver was easily palpable. He did not improve and died eight hours after admission.

Laboratory Data.—At the time of the first admission, the red blood cell count was 1,860,000, and the hemoglobin was 34 per cent. The volume index was 0.86 and the hematocrit was 13. There was marked hypochromia and poikilocytosis, but no macrocytes or nucleated red cells were reported. The count was normal on discharge. On the second admission, the red cell count was 2,700,000 with a hemoglobin of 42 per cent. Thereafter it varied somewhat between these figures and normal but was normal on discharge in April. On the day of death the red cell count was 4,410,000, but the hemoglobin was 11.5 grams. Before discharge from the service, repeated electrocardiograms showed a left bundle-branch block, the time of which was 0.16 second. On the day of death an electrocardiogram also showed a QRS complex of 0.16 second and low to inverted T waves in the limb leads (Fig. 2). All other laboratory data during the various periods of hospitalization were within normal limits. These included sedimentation rates, urinalyses, white blood and differential counts, blood sugar and cholesterol, blood Kahns, and basal metabolic rates.

Autopsy (No. 44-196).—

Anatomical Diagnosis: There were history of chronic hypochromic anemia (etiology undetermined); erythroid hyperplasia of bone marrow; hypertrophy and dilation of heart; minute focal necroses and scars in the left ventricle of the heart; chronic passive congestion of the lungs, liver, spleen, and remaining organs; hydropericardium; bloody pleural effusion (bilateral); ascites; peripheral edema; acute phlebitis of the thyroid vein; multiple thrombotic emboli to the lungs; and multiple infarcts of the lungs.

Body: There was moderate pitting edema of the dependent portions of the body. On section, 500 c.c. of blood-tinged fluid were present in the left pleural cavity and 300 c.c. in the right. In the peritoneal cavity there were 300 c.c. of clear straw-colored fluid. There was ex-

tensive chronic passive congestion of all organs. A small vein external to the capsule of the thyroid was occluded by a thrombus which microscopically was necrotic. Several of the arteries in the lower lobes of both lungs were also occluded by thrombi, which showed no evidence of organization microscopically and which were associated with numerous fresh hemorrhagic infarcts of the lungs. In sections of the ribs and vertebral bodies, the erythropoietic elements were increased in number but were otherwise normal.

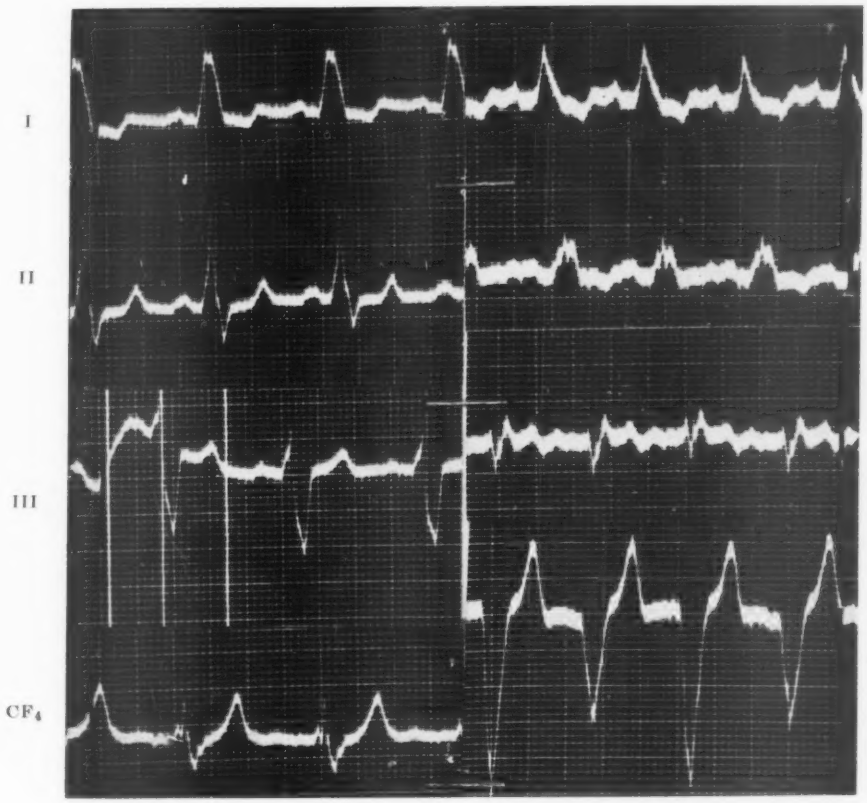

Fig. 2.—Case 2. The QRS interval is 0.16 second in both tracings; on the day of death there are T wave changes.

Heart: The heart weighed 560 grams and the pericardial sac contained 120 c.c. of clear straw-colored fluid. On section of the heart, all of the chambers were dilated and filled with blood. The left ventricle was distinctly hypertrophied but no focal lesions were seen. The valves were all thin and delicate and showed no lesions. The coronary arteries were patent and there were no gross atheromatous plaques in the intima.

Microscopically, numerous sections from both ventricles and the mitral and aortic valves were examined. The myocardium of the left ventricle was diffusely hypertrophied and the endocardium of the left auricle showed patchy fibrous thickening. Scattered in the left ventricle were occasional stellate scars associated with small amounts of round-cell infiltration. In addition, several minute focal necroses together with a few polymorphonuclear leucocytes and lymphocytes were seen. Similar areas of acute inflammatory reaction were seen in the endocardium of the

left ventricle. There were also small areas of necrosis and fibrinoid degeneration of the endocardium. The small branches of the coronary arteries, however, showed no lesions. No other abnormalities were seen.

CASE 3.—

Clinical History.—H. P. E., a Negro man, aged 25 years, was admitted to the Philadelphia Naval Hospital on Jan. 1, 1945, with a chief complaint of periodic shortness of breath. He had enlisted in the United States Navy on April 4, 1938. The past medical and family histories were not informative. He had no illnesses other than minor infections of the upper respiratory tract before his first admission to the sick list.

On Aug. 8, 1944, while engaged in heavy work on one of the tropical islands in the South Pacific, where he had been stationed for several months, he suddenly fell unconscious. He soon regained consciousness, but on admission to the hospital he was objectively dyspneic, and the physical signs were not relieved by the administration of adrenalin and aminophylline. An x-ray film of the chest was normal. He gradually improved, although attacks of dyspnea and cough recurred, and he was evacuated to a hospital in the continental United States. After his arrival, he had no further dyspnea or other symptoms and was discharged to duty on Dec. 24, 1944. The highest blood pressure during this period was 106/70. Six days later, however, paroxysmal dyspnea recurred and he was admitted to this hospital the next day, Jan. 1, 1945.

On admission he was dyspneic, and numerous crackling and sonorous râles were heard over both lungs. The heart was not thought to be enlarged; the rhythm was regular, the rate was 72, and no abnormal sounds were heard. Blood pressure was 98/56. No other physical abnormalities were noted. Within four days, dyspnea at rest subsided, but the exercise tolerance appeared to be less than normal. However, he had no other symptoms until March 7, when he acquired an acute gonococcus urethritis which was satisfactorily treated with penicillin and which did not recur. On March 11, dyspnea while at rest again appeared and edema of the ankles was first observed. From that time until death, symptoms and signs of congestive failure increased in severity, and the heart, by physical and x-ray examination, increased in size. Two days before death he had severe hemoptysis and there were signs of consolidation in both lungs. He died on June 24, 1945.

Laboratory Data.—There were no electrocardiograms on the first admission. On the second admission, repeated electrocardiograms showed constantly changing P-R intervals, T waves varying from flat to the late V type of inversion in all leads, and constantly isoelectric S-T segments. The cardiac rate varied from 66 to 78 (Fig. 3). Blood cultures on Jan. 2, Jan. 8, Feb. 12, and April 16, 1945, were sterile. Except during the episode of urethritis, tests were repeatedly negative for allergy. Other examinations, most of which were repeated on both admissions, were also normal. These included blood Kahns, blood sugar, blood urea nitrogen, urea clearance, blood cholesterol, and total serum protein. Numerous blood smears were negative for malarial parasites and, in wet preparations of the blood, sickling of the red cells was not demonstrated.

Autopsy (No. 45-194).—

Anatomical Diagnosis: There were chronic degeneration and focal scarring of both ventricles of heart; hypertrophy and dilatation of heart; organizing mural thrombi, left ventricle of heart; chronic passive congestion of lungs, liver, spleen, and kidneys; hydropericardium; hydrothorax, bilateral; ascites; peripheral edema; extensive lobular pneumonia.

Body: There were generalized subcutaneous edema, most marked in the dependent parts of the body. On section there were 2,200 c.c. of clear straw-colored fluid in the peritoneal cavity, 200 c.c. in each pleural cavity, and 150 c.c. in the pericardial cavity. The organs all showed extensive chronic passive congestion. Widespread areas of fresh fibrinopurulent exudate were present in both lungs.

Heart: The heart weighed 550 grams. The chambers of the heart were all dilated and filled with clotted blood. In the left ventricle, small gray-red mural thrombi were loosely adherent to the columnae carneae. The endocardium of the left ventricle and left auricle was slightly thickened. The valves were all thin, delicate, and apparently normal. The coronary arteries

were patent and showed only very slight atheromatous changes. The myocardium of both ventricles was pale and flabby, but no focal lesions were seen.

Microscopically, there was patchy hypertrophy of the left ventricle, but in many areas of both ventricles the muscle fibers were small and appeared stretched, and small colorless vacuoles were numerous in the muscle fibers. In some fibers, the vacuoles were so numerous that a honeycomb appearance resulted. The fibrous septa were edematous, and rarely minute collections of lymphocytes, plasma cells, and macrophages were seen. None of these, however, resembled Aschoff bodies. The mural thrombi in the left ventricle were just beginning to organize. In sections of both auricles and of the mitral and aortic valves, no lesions were seen. Special stains for glycogen and fat were not obtained since the only available material was preserved in 80 per cent alcohol. In Gram stains, bacteria were not seen in the thrombi.

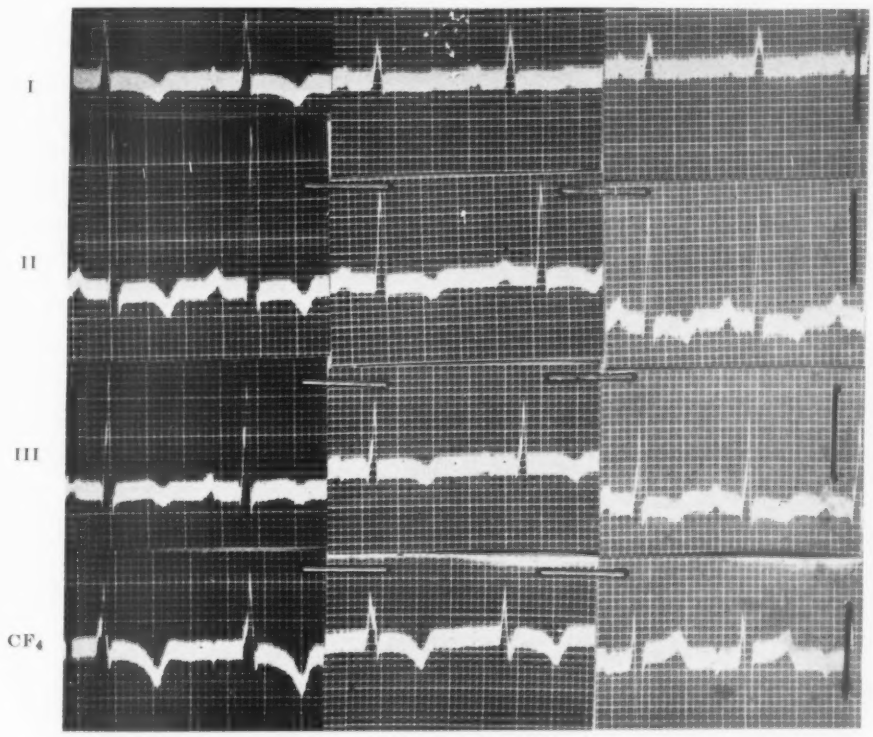

Fig. 3.—Case 3. Throughout the five months of final hospitalization there were constantly changing P-R intervals and varying types of T waves in Leads I, II, and IV, which are shown in the above tracings. The changes in Lead IV may be due to variations in position of the electrodes.

CASE 4.—

Clinical History.—C. W., a white man, aged 29 years, was admitted to the Philadelphia Naval Hospital on June 15, 1945, complaining of vomiting and abdominal pain of four days' duration. The past medical and family histories were irrelevant. He enlisted in the United States Army in August, 1942, and was well until January, 1945, when he was stationed in Oran, Algeria. At that time, he was found wandering about the streets in a state of mental confusion. Upon hospitalization, a diagnosis of amnesia was made, for which he was discharged from the service on April 15, after his return to the continental United States. During this period, an

x-ray film of the chest was reported as normal and the highest blood pressure was 116/80. He then worked as a bellboy until June 11, 1945, when he was taken ill with nausea, vomiting, and cramplike abdominal pains, and was admitted to this hospital four days later.

On admission, he was dyspneic, cyanotic, and jaundiced. There was no peripheral edema, but the superficial veins of the neck were distended. The heart appeared to be moderately enlarged, both on physical and subsequent x-ray examination; the cardiac rate was 120; the rhythm was regular; audible gallop sounds were present; and a soft systolic murmur was localized at the apex. The blood pressure was 90/82. The lungs were not remarkable and the liver and spleen were not at first palpable. Within a day, however, he became mentally confused; numerous crackling râles were heard over both lungs; signs of effusion in the pleural and peritoneal cavities appeared; and the legs became edematous. The jaundice deepened and the liver became palpable. He grew weaker and died on June 24, 1945, nine days after admission.

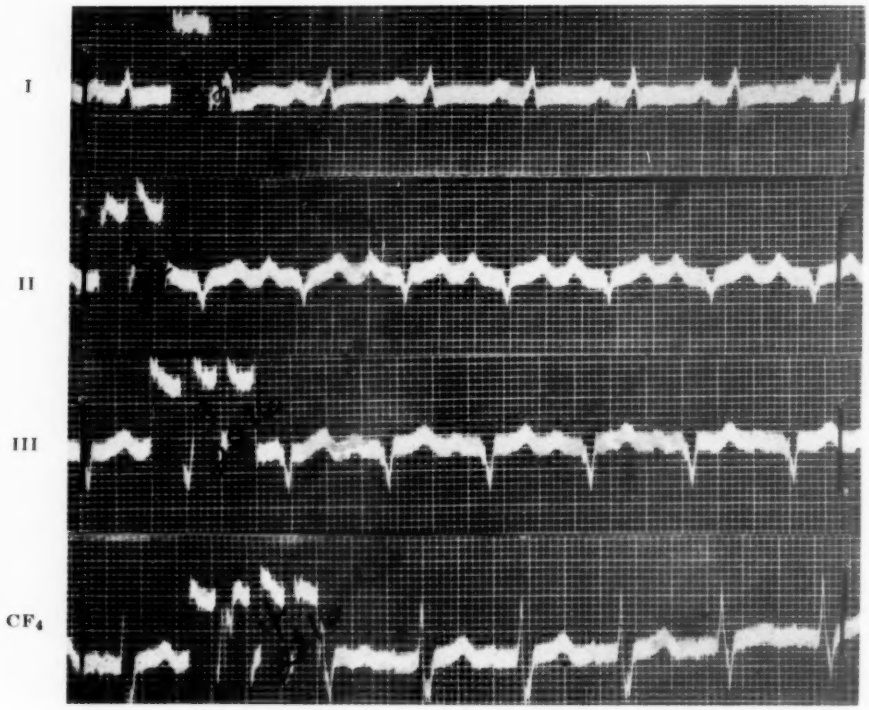

Fig. 4.—Case 4. This tracing taken during the terminal stage of illness shows low voltage QRS complexes in limb leads and the flattened T_1.

Laboratory Data.—On the first admission, electrocardiograms were reported as normal. During the final hospitalization, an electrocardiogram showed a P-R interval of 0.18 second; a QRS complex of 0.07 second and low voltage throughout; and flattened T waves in all leads (Fig. 4). During the first admission, all laboratory tests were normal including repeated smears for malaria, blood Kahns, blood counts, urinalyses, examination of the spinal fluid, electroencephalogram, blood sugar and urea nitrogen, and several basal metabolic rates. During his final illness, urinalyses showed the presence of bile, traces of albumin, and numerous white blood cells. The blood bilirubin, estimated by the van den Bergh method, was 9 mg. per 100 cubic centimeter. The blood urea nitrogen rose from 18 on admission to 82 mg. per 100 c.c. on the day before death. One blood culture was sterile.

Autopsy (No. 45-197).—

Anatomical Diagnosis: There were chronic degeneration of both ventricles of heart; hypertrophy and dilatation of heart; chronic passive congestion of lungs, spleen, liver, and kidneys; hydrothorax, bilateral; ascites; peripheral edema; jaundice; organizing mural thrombi, left vertricle of the heart; embolic thrombus and infarct of the left kidney; organizing thrombi of the prostatic veins; multiple emdolic thrombi of the pulmonary arteries; and multiple infarcts of both lungs.

Body: The lips, mucous membranes, and nail beds were intensely cyanotic. The legs, dependent parts of the body, and the eyelids were edematous. The skin and sclerae were jaundiced. On section, 1,000 c.c. of clear, bile-tinged fluid was present in the abdominal cavity, 1,500 c.c. in the right pleural cavity, and 300 c.c. in the left pleural cavity. The amount of pericardial fluid was not significantly increased. There was marked chronic passive congestion of the organs. A recent small infarct was present in the left kidney. Most of the veins about the prostate were occluded by organizing thrombi. Large hemorrhagic infarcts were present in both lungs and were associated with numerous organizing thrombi in the pulmonary arteries. The liver was markedly engorged with blood and microscopically the central and mid-zonal areas were necrotic and replaced by hemorrhage. Permission was not obtained to examine the brain.

Heart: The heart weighed 450 grams. All of the chambers of the heart were dilated and filled with blood. The left ventricle also was moderately hypertrophied. The valves were all normal. Among the trabeculae of the left ventricle were several small gray-red thrombi which were firmly attached to the underlying endocardium. Elsewhere the endocardium was normal and there were no gross lesions of the myocardium. The coronary arteries were patent and showed only very slight atheromatous changes of the intima.

Microscopically, in sections of both ventricles, groups of muscle fibers, particularly in the left ventricle, were hypertrophied. In most areas, however, the individual fibers were thin and appeared stretched. A few of the hypertrophied fibers contained scattered, clear, colorless elliptical vacuoles within the cytoplasm. This vacuolization was perhaps more conspicuous beneath the endocardium to which were attached the mural thrombi. These thrombi were already deeply invaded by proliferating fibroblasts and lamination was still visible only on the surface. Elsewhere the endocardium was normal. No lesions were seen in either auricle or in sections of the mitral and aortic valves. Since only blocks preserved in 80 per cent alcohol were available, stains for glycogen and fat were unsatisfactory. In Gram stains bacteria were not seen in the thrombi.

DISCUSSION

In a discussion of these cases, it is advisable first to recapitulate the salient clinical features in order to emphasize their differences.

In Case 1, hypertrophy of the heart and symptoms of myocardial insufficiency were first detected soon after an operation for gangrenous appendicities requiring drainage. Convalescence was complicated only by a respiratory tract infection, thought to be pneumonia, which subsided without the administration of sulfonamides. The patient had no further evidence of infection and was afebrile until shortly before death, when bronchopneumonia occurred. Following discharge from the service, because of enlargement of the heart, for which hospitalization was not considered essential, he was examined frequently as an outpatient, but evidence of congestive failure was not recognized until the final admission to this hospital eighteen months afterward and one month before death. In Case 2, congestive heart failure was not recognized until the final admission a few hours before death. The disorder for which the patient was first admitted to the sick list and for which he was subsequently discharged from the service was un-

explained recurrent hypochromic anemia which always responded promptly to treatment. However, the patient himself related the onset of symptoms to an acute infection of the respiratory tract, but this infection was not observed clinically and he remained afebrile throughout the illness. Laboratory data also did not suggest the presence of infection. At first, in Case 3, the patient was thought to have bronchial asthma, and it is possible that he also had acute bronchitis. Except during the attack of acute urethritis, he had no further evidence of infection and was afebrile until the occurrence of terminal bronchopneumonia. The diagnosis of bronchial asthma was subsequently discarded when no evidence of allergy was demonstrated. For at least six months before death, however, incipient congestive failure was recognized clinically and for this reason he was not discharged from the service. In Case 4, the patient was first hospitalized for amnesia of sudden onset and was subsequently discharged with this diagnosis. Two months later, however, he was admitted to this hospital in severe congestive failure and died nine days later. The clinical course was entirely afebrile and laboratory data did not suggest the presence of an infectious disease.

At this point, parenthetically, it is worthy of emphasis that at autopsy the mural thrombi in the left ventricles of Cases 3 and 4 did not resemble the vegetations of bacterial endocarditis. Grossly the surfaces were smooth. The deeper layers, microscopically, were being replaced by fibroblasts and the superficial layers were laminated and not necrotic. Bacteria could not be demonstrated with Gram stains. It is evident, therefore, that only in Case 1 was the onset of symptoms related to the occurrence of an acute infectious disease and in none of the cases was there evidence of any chronic infection. It is equally apparent that the onset of illness and clinical course in each case differed and did not at first suggest a diagnosis of heart disease.

It is interesting that in each patient serious heart disease was not at first recognized as the outstanding abnormality. Only in Case 1 was the diagnosis made early and then only after the patient was discharged to duty following recovery from the appendectomy. In patients of this age, without hypertension or evidence of valvular disease, a diagnosis of heart disease is not ordinarily a prominent consideration. However, in all cases, a thorough survey of the heart was actually made early in the course of the illness. That tests, including electrocardiograms and chest x-ray films, at first gave normal results, except in Case 1, probably explains why a diagnosis of heart disease was temporarily discarded.

The question arises, therefore, when during the illness of each patient heart disease may have occurred. In Case 1, the heart was reported as being enlarged by x-ray examination during convalescence from the appendectomy. This was confirmed during the second admission, but at that time an electrocardiogram was said to be normal. It is quite possible, therefore, that cardiac enlargement may have preceded the appendicitis. In Case 2, enlargement of the heart by x-ray examination and electrocardiographic changes suggestive of myocardial damage were first recognized six to eight months following the onset

of symptoms. There is a distinct possibility, however, that at the time of the first admission, when cough, weakness and dyspnea on exertion were conspicuous symptoms, the patient was already suffering from heart disease. It is also probable that in Case 3, heart disease was responsible for the paroxysmal attacks of cough and dyspnea which at first were diagnosed as bronchial asthma. In Case 4, likewise, the sudden onset of mental confusion less than six months before death may have been caused by emboli from an already damaged heart. In this connection, it will be recalled that at autopsy the mural thrombi in the left ventricle were already extensively organized. From the available evidence, therefore, it is possible that heart disease in all four cases already existed at the time of the first admission to the sick list.

There appears to be little doubt, pathologically, that the principal cause of death in all four cases was congestive heart failure. In the first place, the hearts weighed 890, 560, 550, and 450 grams, respectively. These weights are obviously greater than the limits of normal. In the second place, evidence of marked chronic passive congestion was widespread both grossly and microscopically. In Cases 1 and 3, however, the final illnesses were complicated by terminal bronchopneumonia. Multiple pulmonary emboli and infarcts in Cases 2 and 4 were undoubtedly manifestations of peripheral stasis and thrombosis incident to the congestive failure and almost certainly were important causes in precipitating death.

The jaundice and necrosis of the parenchymal liver cells in Case 4 may have been due to chronic passive congestion and to the destruction of excessive amounts of red blood cells in the pulmonary infarcts, or, to these factors plus an acute infectious hepatitis; the associated uremia was distinctly terminal.

In Cases 3 and 4, the presence of mural thrombi in the left ventricles suggests myocardial infarction, but the coronary arteries grossly and microscopically were not occluded and even microscopically there were no large areas of necrosis. It is much more likely that a combination of stasis of blood flow in the ventricles and small areas of subendocardial degeneration was responsible for these lesions.

As for etiology, it is apparent from the case reports that none of the factors commonly responsible for hypertrophy and dilatation of the heart were present. Thus, there was no evidence of hypertension, coronary arteriosclerosis or thrombosis, valvular disease, congenital defects of the heart, or chronic disease of the lungs. There was no evidence of hyperthyroidism, clinically or pathologically. As far as can be determined, the diets of the patients were adequate and in some instances were supplemented with multiple vitamin preparations. It is very unlikely, therefore, that any of them were suffering from vitamin B deficiency. The possibility of rheumatic myocarditis without valvulitis was considered, but the clinical manifestations of rheumatic fever were lacking and the small foci of round-cell infiltration in the ventricles of Cases 2 and 3 did not resemble Aschoff bodies.

In Case 2, there was recurrent, moderately severe anemia, which was the presenting symptom during most of the illness. It was classified only as being

hypochromic and the etiology was not determined. The response to therapy was prompt, however, and the patient was not severely anemic at death. There is great doubt, therefore, whether an anemia of this extent so affected the heart as to cause hypertrophy and congestive failure. White[5] believed such anemias to be without effect in permanently damaging the heart unless they were severe or prolonged. Nemet and Gross[6] found cardiac hypertrophy to be extremely rare in anemia. Amadeo[7] was equally impressed by the failure of anemia to produce cardiac hypertrophy.

Recently Candel and Wheelock[8] have emphasized the frequency with which acute infections, particularly of the respiratory tract, may be complicated by transient acute myocarditis and have described the electrocardiographic changes which are thought to indicate derangement of the myocardium. But in our cases electrocardiograms were not significantly abnormal early in the illnesses. However, the onset of symptoms in Case 1 did immediately follow an acute infection. Undoubtedly, the remaining patients had upper respiratory tract infections from time to time before the onset of the final illness, but these must have been so mild that hospitalization was unnecessary. The attack of urethritis in Case 3, moreover, occurred long after the onset of cardiac symptoms and, although it may have adversely affected the course of the illness, it certainly was not the cause of it. It is possible that the apparent myocardial damage described by Candel and Wheelock[8] may not always be reversible and may cause cardiac hypertrophy some time afterward; but this concept is so unusual that it can be considered only as a possibility at this time.

Although the present cases are not typical of so-called isolated myocarditis of Fiedler[9] in which extensive inflammation of the myocardium is characteristic, there are points of similarity between the two groups which might justify this classification of our cases. As in isolated myocarditis, so in the present cases, relatively rapid and progressive enlargement of the heart terminated in congestive failure, but evidence of chronic infection was lacking.

In Cases 2 and 3, there were minute, although rare, foci of inflammation in the myocardium, and in Cases 3 and 4, there was also extensive focal vacuolization of the myocardium of the ventricles. These were not so extensive, however, as to constitute an unequivocal diffuse myocarditis, and in Case 1 there was neither vacuolization nor inflammatory exudate. In this case, furthermore, the scarring was no more extensive than is customarily observed in myocardial hypertrophy of this degree from any common cause. Nevertheless, it may be argued that extensive inflammatory exudate was present in the myocardium of the present cases earlier in the course of the disease and had largely disappeared by the time of death. Even if these cases are thought to belong in this group, therefore, one is still far from any conclusion as to etiology. In his recent reviews of the literature, Saphir[10,11] has pointed out not only the variability of extent and character of the inflammatory exudate in the hearts of the reported cases of isolated myocarditis, but also the large number of infections which have been suggested as dubious causes of the disease. Fiedler's myocarditis, consequently,

appears to be a group which includes various disease entities, the etiology of which is just as uncertain as that of the present cases.

It is unfortunate that properly fixed material was not available for glycogen or fat stains in Cases 3 and 4. Although it is highly unlikely that the vacuoles in the muscle fibers were glycogen, or that these cases represent some phase of glycogen-storage disease, it would be satisfying to settle this question. If the lesions were either fatty or hydropic degeneration, as seems more likely, such abnormalities are not specific of any disease entity. Interestingly enough, one of Levy and Rousselot's[1] cases also had extensive vacuolization of the myocardium which was interpreted as hydropic degeneration.

From the preceding discussion, it is evident, therefore, that the cause of the myocardial hypertrophy in each of the four cases presented is obscure, and etiologically these cases may be wholly unrelated.

SUMMARY

1. Four fatal cases of unexplained hypertrophy and dilatation of the heart during the third decade of life are presented. None of the usual causes of hypertrophy were present.

2. The onset of illness differed in individual cases and was not at first recognized as heart disease.

3. Electrocardiograms at first were normal. When changes occurred, the abnormalities suggested only nonspecific myocardial damage.

4. The possible etiologic factors are discussed, but it is not concluded which, if any, were responsible for the cardiac hypertrophy.

5. There is no certainty that the causes of heart disease in the four cases were related.

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PARENTERAL VITAMIN B AS AN AGENT FOR DETERMINING THE ARM-TO-TONGUE CIRCULATION TIME

PART I

ROY E. SWENSON, M.D

PITTSBURGH, PA.

PREVIOUS observations on the velocity of blood flow have been made by using saccharine,[4] calcium salts and magnesium sulfate,[8] and decholin[3] to determine the arm-to-tongue circulation time. Sodium cyanide[12] and alpha lobeline[2,8,10,11] have been used to measure the circulation time from the arm to the carotid sinus. Ether[2,7] has been used to determine the circulation time from the arm to the lung. Papaverine[5] has been utilized to measure the circulation time from the arm to the central nervous system.

The arm-to-tongue circulation time is of clinical value[8] in the diagnosis of congestive heart failure and of those diseases in which the venous return is obstructed. It is also of value in those diseases where the velocity of the blood flow is increased, as in the anemias, hyperthyroidism, and certain febrile states.

Hussey, Cyr, and Katz[8] have summarized the requirements for a suitable agent for determining the circulation time as follows:

1. It must be nontoxic in the dosage used.
2. It must have no undesirable effect upon the condition being studied.
3. There must be a minimum of unpleasant side effects.
4. It must be eliminated rapidly so that it can be used repeatedly.
5. It must have an end point that is easily recognized by the patient.
6. It should be readily available at a low price.

The results of the work to be reported indicate that the vitamin B complex when given intravenously meets all of these conditions.

The use of the vitamin B complex as an agent to determine the arm-to-tongue circulation time was suggested when the complex was given intravenously to an obstetric patient three days post partum. She complained of a taste on her tongue similar to that of a "chewed-up vitamin tablet." The complex was then given to other patients who also tasted it. These observations led to further study of its value in estimating circulation time.

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The preparation used in this study had the following composition*:

Thiamine hydrochloride	10.0 mg.
Riboflavin	10.0 mg.
Pyridoxine hydrochloride	5.0 mg.
Calcium pantothenate	50.0 mg.
Nicotinamide	250.0 mg.

These amounts were contained in 5.0 c.c. of sterile isotonic saline solution. Five cubic centimeters were used for each determination. A duplicate determination was made within a few seconds of the initial one. Each subject, therefore, received a total of twice the amount of the drugs listed.

The normal serum concentration of thiamine hydrochloride is from 0.2 to 2.0 μg per 100 c.c.,[14] and the intravenous administration of 50 mg. of the substance elevates this level to from 130 to 200 μg within five minutes. This falls to from 5 to 15 μg within an hour, for the substance is almost immediately excreted. Large doses have been given to rats and dogs without any toxic effect being noted in the electrocardiograms.[6] From 26 to 68 per cent of a 16 mg. test dose of riboflavin given intravenously is excreted within four hours, and there is little storage of the substance.[13,14] Pyridoxine hydrochloride and calcium pantothenate are rapidly excreted.[16,17] The intravenous administration of 5 mg. of nicotinic acid per kilogram in man increases the normal whole blood concentration from 0.25 to 0.89 mg. per 100 c.c. to a maximum of 130 mg. per cent; this falls to normal in two hours as conjugates are excreted in the urine.[14,18] In the literature reviewed, no variations in the pulse or blood pressure were reported after the administration of these substances in the dosages given.

TECHNIQUE

The patient was placed in a semirecumbent position and the left arm was supported at the approximate level of the right auricle. A tourniquet was then applied above the antecubital fossa. Sterile 10 c.c. syringes and No. 20 needles were used. After the needle was inserted into one of the antecubital veins, the tourniquet loosened, and venous flow re-established, 5 c.c. of the solution were rapidly injected. Time was started on a stop watch at the beginning of the injection. When the patient stated that he tasted the substance, time was stopped, but the needle was left in the vein. When he no longer tasted the substance, a duplicate determination was made and the needle removed.

The taste on the tongue was described as follows:

1. A taste like that of a brewers' yeast tablet.
2. A taste similar to that of a vitamin tablet.
3. A stale, fishy taste and odor.
4. A warm sensation on the tongue and in the throat.

Interns and nurses who received the substance stated that the taste and odor were unmistakable and that the onset of the taste was abrupt and intense.

*The commercial preparation, "Solu-B," manufactured by The Upjohn Co., Kalamazoo, Mich., was used. The Upjohn Company generously supplied the Solu-B used in this work.

RESULTS

Obviously this test would have more practical value and the observations reported would be of greater scientific interest if it could be established that a single component produces the taste sensation. Further study of this aspect of the problem is in progress.

Arm-to-tongue circulation times were determined on fifty normal subjects from various age groups. No circulatory abnormalities were recognized or suspected in any of them. Table I summarizes the control group. The average times of the fifty control subjects as a single group varied from 9.8 to 10.3 seconds for the initial and duplicate determinations, respectively.

TABLE I. AVERAGE ARM-TO-TONGUE CIRCULATION TIMES OF NORMAL CONTROLS

NUMBER OF PATIENTS	AGE GROUP IN YEARS	CIRCULATION TIME IN SECONDS		DEVIATIONS IN SECONDS	
		FIRST	DUPLICATE	FIRST	DUPLICATE
16	16–30	8.7	9.7	−2, +4	±3
16	30–40	10.1	10.5	±4	±4
18	40–	10.7	10.7	±3.3	±3

Estimates of circulation time were made on fifty-two patients with cardiac disease. The cases were studied in four groups. Table II summarizes the results obtained in three groups in which congestive failure was present. Table III summarizes the fourth group in which there was heart disease without congestive failure.

TABLE II. AVERAGE ARM-TO-TONGUE CIRCULATION TIMES OF PATIENTS WITH CONGESTIVE FAILURES

NUMBER OF PATIENTS	DISEASE PROCESS	CIRCULATION TIME IN SECONDS		DEVIATIONS IN RANGE IN SECONDS	
		FIRST	DUPLICATE	FIRST	DUPLICATE
15	Congestive failure; no treatment	34.8	34.6	28–53	27–49
14	Congestive failure; digitalized but not controlled*	22.7	23.1	14.1–46.7	13.5–39.9
10	Congestive failure; digitalized and controlled†	11.8	11.8	9.8–13.4	9.0–15.1

*Patients had received only 0.7 Gm. of digitalis.
†Patients had received at least 1.4 Gm. of digitalis.

TABLE III. ARM-TO-TONGUE CIRCULATION TIMES OF PATIENTS WITH CARDIAC DISEASE BUT WITHOUT CONGESTIVE HEART FAILURE

CASE	DISEASE	CIRCULATION TIME	
		FIRST	DUPLICATE
1	S. B. E.; mitral stenosis	10.1	10.2
2	S. B. E.; mitral stenosis	12.5	14.3
3	Hypertension	9.9	10.8
4	Constrictive pericarditis, after pericardiectomy	12.2	10.0
5	Hypertension; auricular fibrillation	17.0	21.5
6	Coronary occlusion after two weeks	10.0	10.0
7	Hypertensive heart disease; cerebrovascular accident	16.2	15.6
8	Hypertensive encephalopathy; hypertension	9.1	9.4
9	Coronary occlusion	20.0	23.4
10	Arteriosclerosis heart disease; auricular fibrillation; digitalized	10.3	11.0
11	Arteriosclerosis, hypertension; auricular fibrillation; ventricular aneurysm	19.2	16.8
12	Hypertension; aortic stenosis	10.5	12.0
13	Arteriosclerosis; auricular fibrillation	31.0	32.5

The longest circulation times were recorded in those patients in whom congestive failure was severe and untreated. The times were also increased in those patients whose failure had been treated but not controlled. Those who were treated and whose failure had been clinically controlled had times that approached the normal range, although few were actually within normal limits.

Patients who received this vitamin B preparation had few side reactions. Two complained of epigastric fullness, and four stated that they felt unusually warm. One patient complained of bladder tenesmus twenty-four hours after the injection. No other side effects were noted.

SUMMARY

1. The arm-to-tongue circulation time using parenteral vitamin B as the test agent has been determined on fifty normal subjects. In this control group the average time was found to vary from 9.8 to 10.3 seconds for the initial and duplicate determinations, respectively.

2. Similar determinations were also made on a group of fifty-two patients with cardiac disease. It was found that the circulation times determined by this method parallel the times reported for other test agents.

3. The vitamin B preparation used appears to be nontoxic, has little effect upon circulatory dynamics, is readily available, is eliminated rapidly, and has an abrupt end point. The side reactions are minimal. This preparation, therefore, meets the requirements for a satisfactory agent for the determination of the arm-to-tongue circulation time.

4. Studies are now being made to determine which components of the B complex are responsible for the distinctive end point.

Appreciation is expressed to Dr. W. L. Mullins, cardiologist of the Mercy Hospital, Pittsburgh, Pa., for many helpful suggestions.

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THE COMBINED USE OF LANATOSIDE C AND QUINIDINE SULFATE IN THE ABOLITION OF ESTABLISHED AURICULAR FLUTTER

RALPH M. TANDOWSKY, M.D., JOSEPH M. OYSTER, M.D., AND ALEXANDER SILVERGLADE, M.D.
LOS ANGELES, CALIF.

DIGITALIS leaf and quinidine have been recommended, singly and in combination, for the abolition of auricular flutter.[1] We have not obtained consistent results by this method of therapy. One reason is that this arrhythmia frequently undergoes spontaneous reversion to a normal mechanism in both treated and untreated cases. In a study embracing the use of these drugs, this clinical inconsistency may be greatly obviated by using as test subjects patients with established auricular flutter who have failed to respond to various methods of therapy for a period of not less than three days. Furthermore, a better pharmacologic understanding of both quinidine and digitalis is essential so that the careful choice of each in proper dosage and sequence will result in therapeutic effectiveness. Heretofore, with the exception of auricular fibrillation, the use of drugs in the conversion of the various arrhythmias has not been based upon sound therapeutic principles.

The action of both quinidine and digitalis on the heart muscle and its neuromechanism is varied and not without complicating factors. Quinidine, for example, reduces vagal tone indirectly, while its direct effect is to depress conduction in auricular muscle. Thus, indirectly it improves conduction and directly this function is depressed; its paralyzing action on the vagus nerve improves conduction, while its action on the auricular muscle increases the refractory period, thus prolonging the duration of the circus wave. A-V conduction under its influence may be variable.[2] This variability of quinidine action has led many to recommend digitalis as the preferable drug in the treatment of supraventricular tachycardia.[3] It is through effects such as these that quinidine slows the circus rate in auricular fibrillation.[4, 5] Its action when a mechanism other than auricular fibrillation is present is difficult to predict. This leads us to believe that the use of quinidine in the treatment of auricular flutter is unsound therapy, while in the presence of auricular fibrillation its value has been clearly established.

Digitalis, on the other hand, exerts a stimulating vagus effect[6] which shortens the refractory period. Its direct muscular action slows conduction in auricular muscle by increasing the refractory period. Vagal action is more marked than the direct effect on the auricular musculature and the usual result, therefore, is

From the Department of Medicine of the College of Medical Evangelists and the Medical Service of the Los Angeles County General Hospital.
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an increase in the rate and irregularity of the circus movement. In addition to its effect on the vagus and the auricles, digitalis produces a slowing effect on the ventricles by direct and indirect depression of the A-V node. The combined effects of digitalis are an effect on the refractory period of auricular muscle, which acts toward converting auricular flutter into auricular fibrillation, and depression of A-V conduction.[8]

Lanatoside C,* by its strong vagus influence, in our experience has been especially effectual in slowing the heart rate. Its rapidity of action, in our opinion, accounts for its strong vagus effect, and this action is far superior to other forms of digitalis in common use.[7] Rapid slowing of the ventricular rate has been the rule in the presence of auricular flutter when lanatoside C is used; of especial interest has been our frequent observance of the conversion of auricular flutter to auricular fibrillation following this slowing effect. When slowing of the heart rate and restoration of normal rhythm occurs, we may attribute this effect to the combined action of digitalis upon the auricular muscle and nodal tissue.[9]

Digitalis, particularly when given by the oral route, often fails to produce effective cardiac response in the presence of auricular flutter and other supraventricular arrhythmias, particularly in the presence of congestive heart failure.[10] Improper assimilation from a digestive tract is probably the causative factor.

Lanatoside C, when given intravenously, has many advantages over oral digitalis, particularly if immediate action is essential. We have demonstrated its rapid action in auricular flutter, clinically and electrocardiographically, in those with and without congestive heart failure.[10] Lanatoside C, when given intravenously, will, on occasion, convert auricular flutter to sinus rhythm. This conversion, however, is inconsistent when this arrhythmia has obtained for many days. Conversion of auricular flutter to auricular fibrillation by the intravenous use of lanatoside C is seen quite consistently in those patients whose auricular flutter has been established for three or more days. Once auricular fibrillation makes its appearance, the use of quinidine may be of definite therapeutic value for the conversion of the arrhythmia to sinus rhythm. Lanatoside C may be given in full therapeutic dosage, quickly, by the intravenous route, with a minimum of untoward symptoms.[11, 12] It has also been shown to be of value prophylactically when sinus rhythm returns.[13]

METHOD AND PROCEDURE

This study embraces the use of both lanatoside C and quinidine sulfate in sequence. Lanatoside C was given intravenously in full digitalizing dosage (1.6 mg.). The effects were maintained by the administration of 1 mg. daily. Quinidine sulfate was used in varying dosage, depending upon individual requirements and tolerance (.72 to 1.44 Gm.).

After the diagnosis of auricular flutter was established clinically and electrocardiographically, historical data were carefully studied to determine the quantity and type of previous medication. Patients who received digitalis in appreci-

*Commercially marketed as Cedilanid by the Sandoz Chemical Works, Inc., New York, N. Y.

able quantities just prior to admission were eliminated from the series. The subjects included in this study were chosen irrespective of age, sex, race, and complicating disease. All were hospitalized. Following the intravenous administration of lanatoside C, frequent serial electrocardiograms were obtained, and clinical examination was made at frequent intervals. As soon as the diagnosis of auricular fibrillation was established, quinidine sulfate was given orally with a maintenance dosage of lanatoside C. When sinus rhythm was established, the quinidine was discontinued but the prophylactic dosage of lanatoside C was continued. In some of the group, other forms of supportive therapy were used, depending upon the underlying symptoms and disease.

RESULTS

Sixteen men and five women constituted the series of patients studied (Table I and Figs. 1, 2, 3, and 4). The diagnosis of auricular flutter was clearly established by the electrocardiograph in all twenty-one patients. The ventricular rates ranged from 140 to 200 per minute. The duration of auricular flutter prior to admission varied from three to twenty-eight days, with an average pretherapeutic duration of approximately fifteen days. This computation had to be based mainly upon information given by the patients and may not be entirely reliable. The age of the twenty-one patients ranged from 30 to 75 years. The average age was 57 years.

Three of the twenty-one patients showed no evidence of pre-existing disease. In the remaining eighteen patients there was associated disease which was diagnostically classified as hypertensive cardiovascular disease in nine patients, rheumatic heart disease in four, arteriosclerosis in two, thryotoxicosis in one, coronary atherosclerosis in one, and alcoholism with complicating bronchopneumonia in one. In three patients, early congestive heart failure was evident.

Twelve of the twenty-one patients had received no specific therapy. Four of the entire group had received full doses of digitalis and had received maintenance doses of this drug for a number of weeks before the present study was undertaken. Three patients had received digitalis and quinidine, and two had received quinidine alone. None of these nine treated patients had been helped by the therapy they had received.

Following the intravenous administration of lanatoside C to the twenty-one patients under observation, a primary slowing of the ventricular rate occurred within one hour. In four, the primary slowing of the ventricular rate was lacking. In one of these four patients, a slow sinus rhythm was established within twenty minutes. In four of the entire group, sinus rhythm was established without any medication other than the initial dosage of lanatoside C. The time needed for this conversion varied from twenty to sixty minutes. Auricular fibrillation was established after the administration of lanatoside C in fifteen of the group in from two to seventy-two hours. In one patient auricular flutter continued for thirteen days before auricular fibrillation was established. In one patient the flutter was not converted to either auricular fibrillation or sinus rhythm. This patient suffered from thyrotoxicosis and was eventually treated by surgery.

TABLE I. RESULTS OF THE COMBINED USE OF LANATOSIDE C AND QUINIDINE SULFATE IN THE TREATMENT OF TWENTY-ONE PATIENTS WITH AURICULAR FLUTTER

CASE	AGE	SEX	DIAGNOSIS		SYMPTOMS			PREVIOUS MEDICATION	EFFECT OF PREVIOUS MEDICATION	LANOTOSIDE C DOSAGE IN MG.	LANATOSIDE C RESULT		ORAL QUINIDINE DOSAGE	QUINIDINE RESULT		FOLLOW-UP THERAPY	RESULT OF THERAPY	DURATION OF S. R.	REMARKS
			CLINICAL	ECG	DURATION	SUBJ.	OBJ.				IMMED.	LATENT		IMMED.	LATENT				
1 (W. R.)	64	M	H. Cv. D.	A. Fl.; V.R., 200	14 days	Dysp.; palp.	L. H. F. (Early)	Dig. leaf, 20 gr.	None	1.6 I.V. plus 1 mg. daily	None	A. Fib. in 140 min.	3 gr. every 6 hr.	None	S.R. in 96 hr.	Dig. leaf, 1½ gr. daily	C.H.F. improved	10 mo.	Readmitted 10 mo. later with gangrene of leg; expired 24 days later from C. V.A.
2 (G. B.)	67	M	H.Cv. D.	A.Fl.; V.R., 140	16 days	Palp.	Tachy.	None	None	1.6 I.V. plus 1 mg. daily	Ventricular rate slowed	S.R. in 50 min.	None	None	None	Lanat. C, ½ mg. daily	Good	24 mo.	Seen 6 mo. later with mild C.H.F.; improved with 1 mg. lanat. C daily
3 (L. M.)	45	M	H.Cv. D.	A.Fl.; V.R., 140	12 days	Dysp.; palp.	Tachy., Br. Asth.	Dig. leaf, 24 gr.; quinidine, 60 gr.	Nausea and cinchonism	1.6 I.V. plus 2 mg. daily	Ventricular rate slowed	A. Fib. in 72 hr.	6 gr. every Q 6 hr.	None	S.R. in 24 hr.	Lanat. C, 1 mg. daily	Good	16 mo.	Follow-up treatment for Br. Asth.
4 (J. McC.)	58	M	R.H.D.	A.Fl.; V.R., 170	16 days	Dysp.	L.H.F.	Dig. leaf, 12 gr.	Nausea	1.6 I.V. plus 1 mg. daily	Ventricular rate slowed	A. Fib. in 12 hr.	Patient intolerant to quinidine	None	None	Dig. leaf, 1½ gr. daily	Partial conversion	A. Fib. obtained	A. Fib. continued until discharged 4 wk. later
5 (L. G.)	30	M	Thyrotox.	A.Fl.; V.R., 140	24 days	Dysp.; palp.	L.H.F. (Mild)	Lugol's solution; deracil. quinidine, 72 gr.	None	1.6 I.V. repeated in 3 days; then 1 mg. daily	None	None	None	None	None	Surgical	Nontherapeutic	Unknown	Thyrotox.; resistant to lanat. C and quinidine
6 (V. R.)	51	F	R.H.D.	A.Fl.; V.R., 150	3 days	Dysp.; palp.; cough	C.H.F. (Early)	None	None	1.6 I.V.plus 1 mg. daily	Ventricular rate slowed	A. Fib. in 24 hr.	20 gr. daily	None	S.R. in 12 hr.	Lenat. C, ½ mg. daily	Good	20 mo.	None

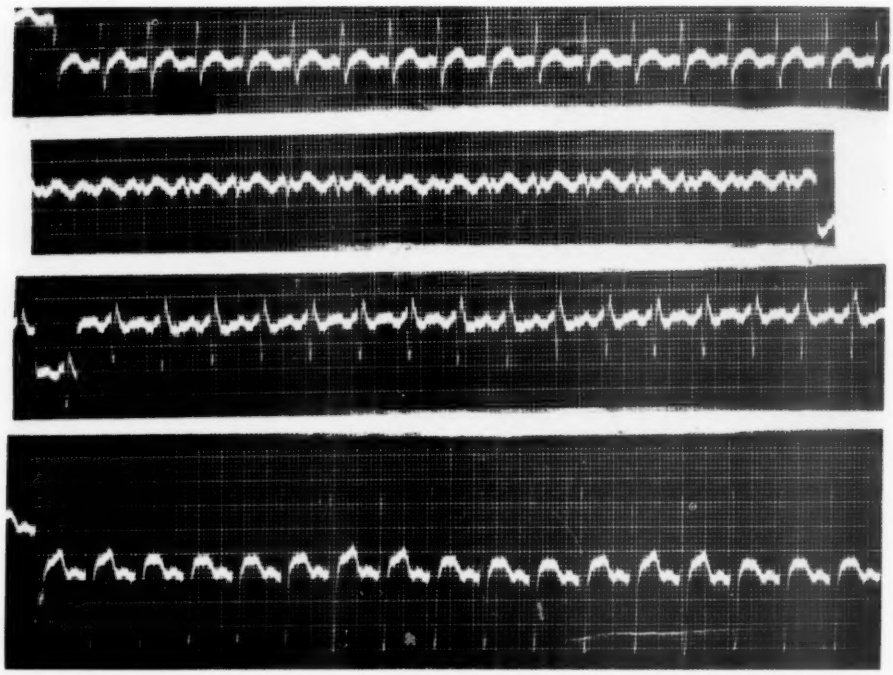
7 (E. M.)	76	F	H.Cv. D.	A.Fl.; V.R., 152	16 days	P. pain; dysp.; palp.	Coron. scl.	Nitro-glycer-ine, P.R.N.	Relief of pain	1.6 I.V. plus 1 mg. daily	Ventri-cular rate slowed	A. Fib. in 20 hr.	20 gr. daily	None	S.R. in 32 hr.	Lanat. C, 1 mg. daily	Good	14 mo.	Expired 14 mo. after therapy from C.V.A.
8 (M. S.)	51	M	None	A.Fl.; V.R., 160	17 days	Palp.	Tachy.	Quinidine, 120 gr.	None	1.6 I.V. plus 1 mg. daily	S.R. in 20 min.	None	None	None	None	Lanat. C, 1 mg. daily	Good	34 mo.	This patient had many attacks of A. Fl. previous to the institution of treatment
9 (A. H.)	49	F	R.H.D.	A.Fl.; V.R., 152	15 days	Palp.; dysp.	Mit. Sten., C.H.F. (mild)	Dig. leaf, 22 gr.	None	1.6 I.V. plus 1 mg. daily	Ventric-ular rate slowed	A. Fib. in 2 hr.	20 gr. daily	None	S.R. in 36 hr.	Lanat. C, 1 mg. daily	Good	26 mo.	None
10 (A. K.)	45	M	R.H.D.	A.Fl.; V.R., 200; V.P.C.	12 days	Palp.; P. pain	C.H.F.	Quinidine, dig. leaf (quanity un-known)	None	1.6 I.V. plus Dig., 1. 3 gr. daily	Ventric-ular rate slowed	S.R. in 1 hr.	None	None	None	Dig. leaf, 3 gr. daily	Poor; recur-rence in 2 wk.	Un-stable	Eight recurrences of A. Fl. in 7 mo. following primary therapy
11 (D. I.)	74	M	None made	A.Fl.; V.R., 160; L B.B.B.	21 days	Palp.; dysp.; syn-cope	L.H.F.	None	None	1.6 I.V. plus 1 mg. daily	Ventric-ular rate slowed	A. Fib. in 2 hr., 50 min.	20 gr. daily	None	S.R. in 24 hr.	Lanat. C, 1 mg. daily	Good	8 mo.	None
12 (E. McP.)	75	M	H.Cv. D.	A.Fl.; V.R., 170	8 days	Palp.; dysp.	L.H.F., Diab. mel. with gang.	None	None	1.6 I.V.	Ventric-ular rate slowed	S.R. in 1 hr.	None	None	None	Lanat. C, 1 mg. daily	Good	10 days	Patient had supra-condylar amputa-tion for gangrene; expired 10 days later
13 (J. M.)	66	M	H.Cv. D.	A.Fl.; V.R., 150	20 days	Dysp.	C.H.F. (severe)	None	None	1.6 I.V. plus 2 mg. daily	Ventric-ular rate slowed	2-1 A-V block, in 2 hr.; S.R., in 24 hr.	None	None	None	Lanat. C, 1 mg. daily	Good	12 mo.	Dismissed fully com-pensated 20 days after entry
14 (E. T.)	61	M	Coron. H.D.	A.Fl.; V.R., 150	10 days	Dysp.	C.H.F., edema	None	None	1.6 I.V. plus 2 mg. daily	Ventric-ular rate slowed	A. Fib., in 24 hr.	24 gr. daily	None	S.R. in 48 hr.	Lanat. C, 1 mg. daily	Good	7 mo.	Patient had previous coronary occlusion and developed C.H. F. after intractable flutter

TABLE I. RESULTS OF THE COMBINED USE OF LANATOSIDE C AND QUINIDINE SULFATE IN THE TREATMENT OF TWENTY-ONE PATIENTS WITH AURICULAR FLUTTER—CONT'D

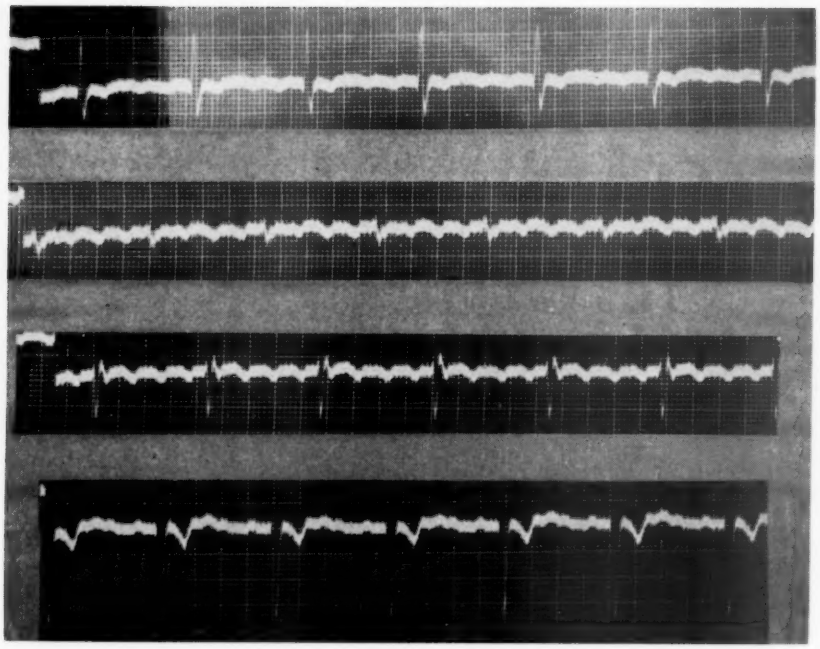
CASE	AGE	SEX	DIAGNOSIS		SYMPTOMS			PREVIOUS MEDICATION	EFFECT OF PREVIOUS MEDICATION	LANOTOSIDE C DOSAGE IN MG.	LANATOSIDE C RESULT		ORAL QUINIDINE DOSAGE	QUINIDINE RESULT		FOLLOW-UP THERAPY	RESULT OF THERAPY	DURATION OF S. R.	REMARKS
			CLINICAL	ECG	DURATION	SUBJ.	OBJ.				IMMED.	LATENT		IMMED.	LATENT				
15 (R. S.)	65	F	H.Cv. D.	A.Fl.; V.R., 160	6 days	Weak; palp.	Tachy.	None	None	1.6 I.V. plus 1 mg. daily	Ventricular rate slowed	A. Fib., in 24 hr.	24 gr. daily	None	S.R. in 72 hr.	Dig. leaf, 1½ gr. daily	Good	4 mo.	None
16 (J. K.)	57	M	H.Cv. D.; gout; Br. Asth.	A.Fl.; V.R., 140	10 days	Dysp.	C.H.F. (Severe)	None	None	1.6 I.V. plus 2 mg. daily	Ventricular rate slowed	A. Fib., 13 days later	18 gr. daily	None	S.R. 10 days later	Lanat. C, 1 mg. daily	Delayed but good	9 mo.	Drug action extremely slow
17 (E. C.)	54	M	None	A.Fl.; V.R., 152	28 days	Dysp.	C.H.F. (Mild)	None	None	1.6 I.V. plus 1 mg. daily	Ventricular rate slowed	A. Fib. in 24 hr.	24 gr. daily	None	S.R. 7 days later	Lanat. C, 2 mg. daily	Good	4 mo.	Slow conversion of A. Fib. to S.R.
18 (P. H.)	54	M	Alcoholism and Br.Pn.	A.Fl.; V.R., 156	25 days	Weak; dysp.; syncope	Br. Pn.	Dig. leaf, 34 gr.	None	1.6 I.V. plus 1.5 daily	Ventricular rate slowed	A. Fib. in 48 hr.	12 gr. daily	None	S.R. 24 hr. later	Lanat. C, 1 mg. daily	Good	6 mo.	None

19 (J. H.)	41	M	None	A.Fl.; V.R., 150	12 days	Weak; dysp.; P. pain	Tachy.	Quinidine, dig. leaf, mecholyl (amount unknown)	None	1.6 I.V. plus 2 mg. daily	Ventricular rate slowed	A. Fib. in 12 hr.	24 gr. daily	None	S.R. in 16 hr.	Lanat. C, 1 mg. daily	Good	5 mo.	Many previous attacks of A. Fl.
20 (M. S.)	62	M	Art. Scl. H.D.	A.Fl.; V.R., 146	9 days	Palp.; weak; dysp.; P. pain	Tachy., C.H.F. (mild)	None	None	1.6 I.V. plus 1.5 daily	Ventricular rate slowed	A. Fib. in 24 hr.	36 gr. daily	None	S.R. in 36 hr.	Lanat. C, 1 mg. daily	Good	2 mo.	Expired of myocardial infarct. approx. 60 days after S.R. was established
21 (J. K.)	65	M	Art. Scl. H.D.	A.Fl.; V.R., 160	14 days	Weak; palp.; dysp.	Coron. anoxia	None	None	1.6 I.V. plus 2 mg. daily	Nodal tachy. V. es.	A. Fib. in 6 hr.	20 gr. daily	None	S.R. in 2 hr. followed by nodal tachy. 6 hr. later	Mecholyl, 0.35 Gm.	Poor	2 hr.	Expired of myocardial infarct. involving septum

A. Fl., Auricular flutter; A. Fib., auricular fibrillation; S.R., sinus rhythm; V.R., ventricular rate; V.P.C., ventricular premature contraction; L.B.B.B., left bundle branch block; C.H.F., congestive heart failure; L.H.F., left heart failure; R.H.D., rheumatic heart disease; H.Cv.D., hypertensive cardiovascular disease; I.V., intravenously; Br. Pn., bronchopneumonia; C.V.A., cardiovascular accident; P. pain, precordial pain; V. es., ventricular extrasystoles.

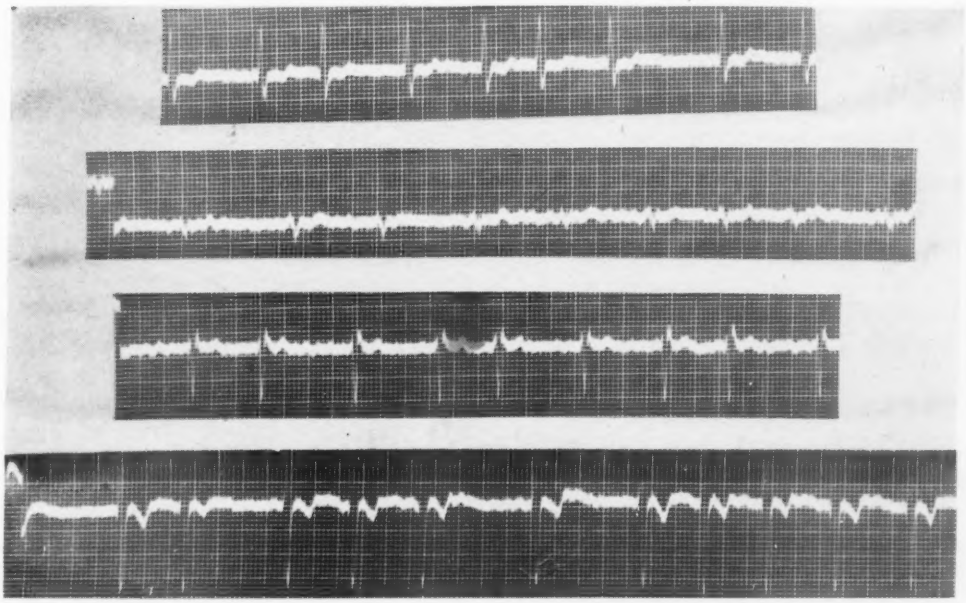


A.

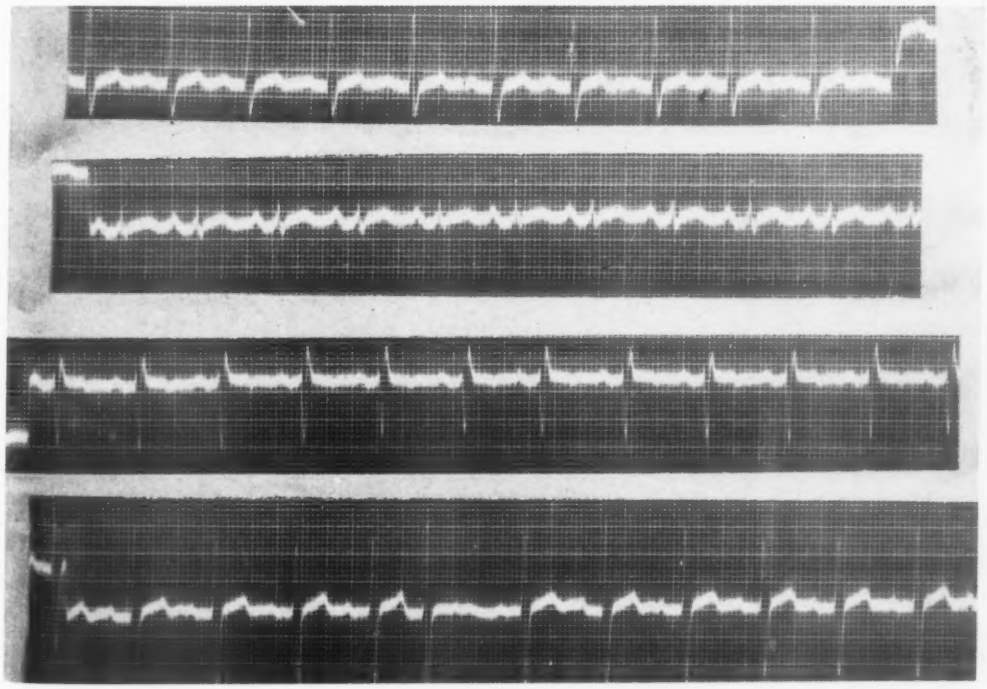


B.

Fig. 1.—Case 3. Conversion of auricular flutter in the presence of associated disease. *A*, Auricular flutter with 2 to 1 A-V block. Ventricular rate, 140 per minute. *B*, Increased A-V block four hours following 1.6 mg. of lanatoside C intravenously. *C*, Demonstrating auricular fibrillation seventy-two hours after initial dosage of lanatoside. *D*, Restoration of sinus rhythm twenty-four hours after quinidine administration. Total dosage, 24 grains.

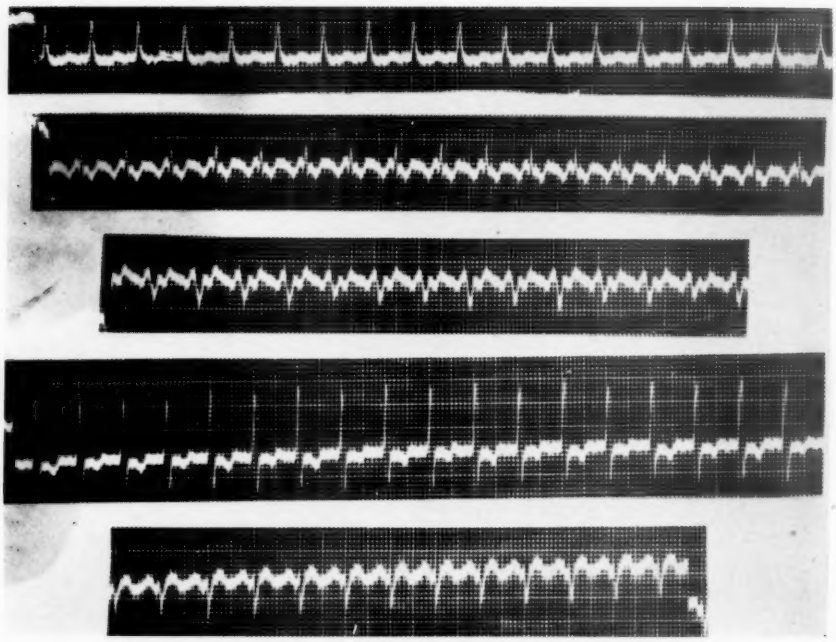


C.

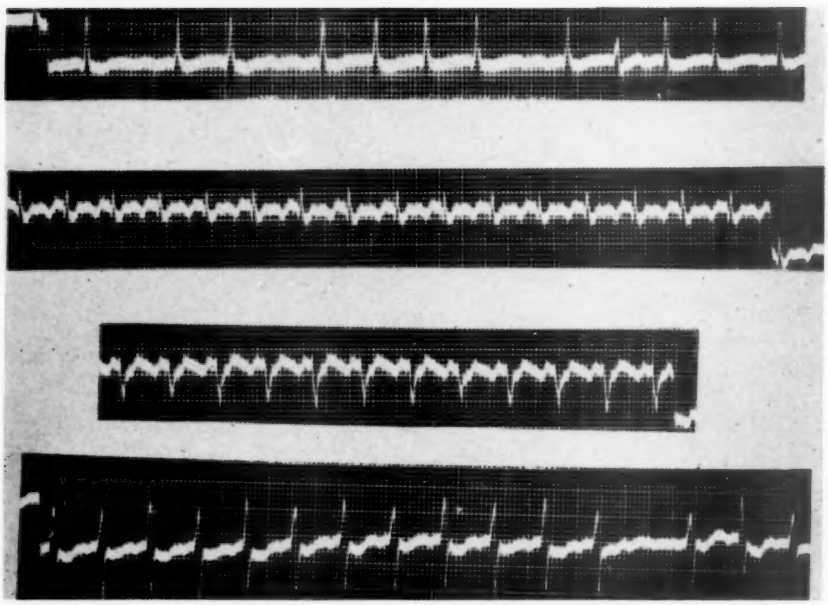


D.

Fig. 1 (Cont'd).—*For complete legend, see opposite page.*

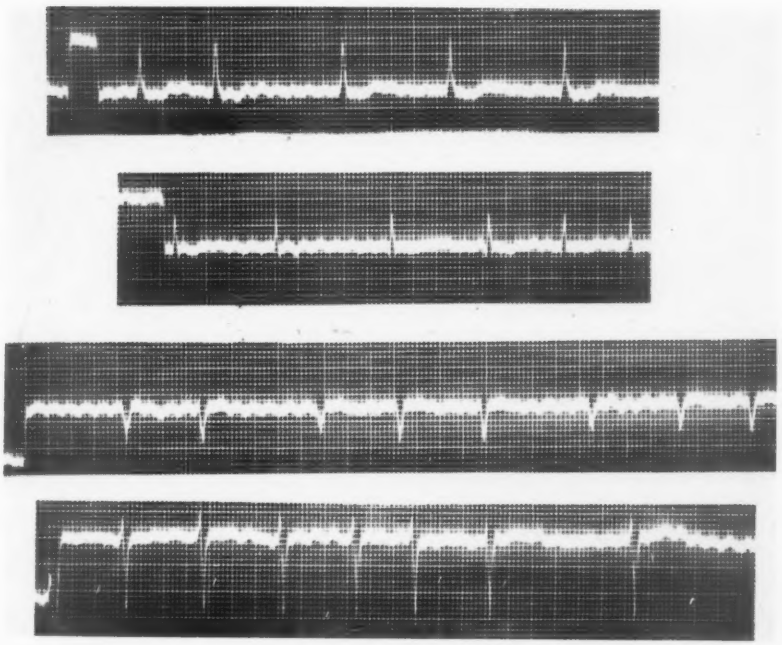


A.

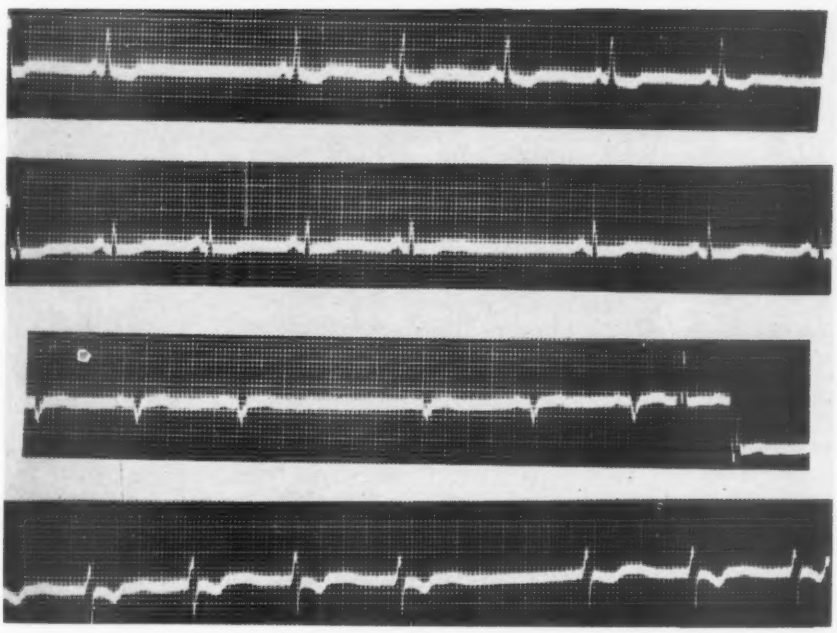


B.

Fig. 2.—Case 19. Conversion of auricular flutter by lanatoside C and quinidine. *A*, Auricular flutter with 2 to 1 A-V block. Ventricular rate, 150 per minute. *B*, Thirty minutes after 1.6 mg. of lanatoside C intravenously. Note slowing effect with increased A-V block. *C*, Conversion to auricular fibrillation twelve hours after initial dosage of lanatoside C. *D*, Restoration of sinus rhythm sixteen hours after administration of 24 gr. of quinidine. *E*, Tracing twenty-four hours after conversion to sinus rhythm. Patient receiving 1 mg. of lanatoside C daily. Voltage has increased and slight left ventricular strain has made its appearance.



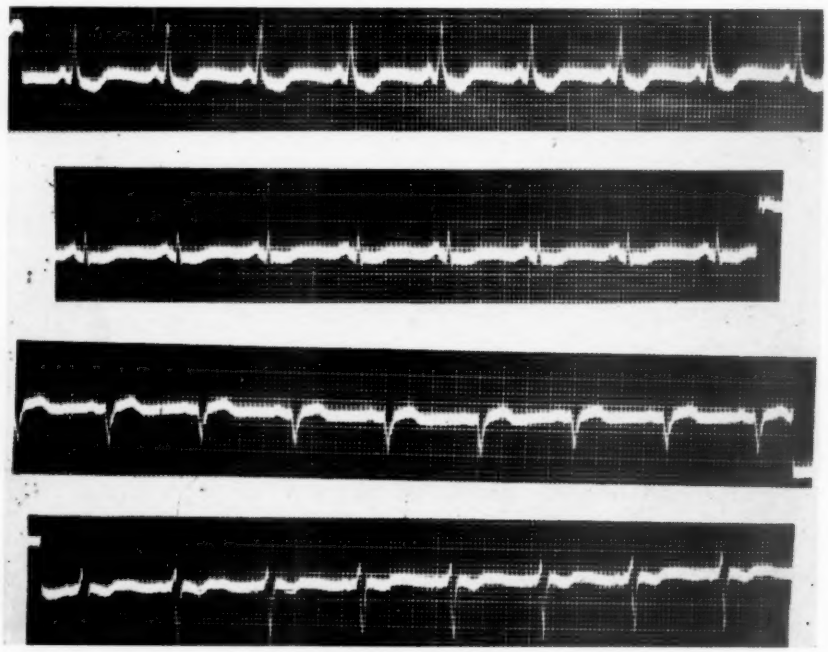
C.



D.

Fig. 2 (Cont'd).—*For complete legend, see opposite page.*

Quinidine sulfate was given orally to fifteen of those in whom auricular flutter was converted into auricular fibrillation. In addition, a maintenance dosage of lanatoside C, consisting of 1 mg. daily, was given. One patient was intolerant to quinidine and the drug had to be discontinued. In the remaining fourteen patients of this group, auricular fibrillation was successfully converted to sinus rhythm over a period of from twelve hours to ten days. The dosage of quinidine was based on individual tolerance and clinical results, and varied from 0.72 to 1.44 Gm. in twenty-four hours. In one patient the auricular flutter recurred immediately after the quinidine was discontinued. This patient had chronic rheumatic heart disease with a history of multiple attacks of auricular paroxysmal tachycardia and auricular flutter since childhood. In another, sinus rhythm was followed by nodal tachycardia and sudden death. Autopsy revealed the presence of an extensive myocardial infarct involving the interventricular septum and a portion of the interauricular septum.



E.

Fig. 2 (Cont'd).—*For complete legend, see page 626.*

The entire group of patients with successfully restored sinus rhythm received a maintenance dosage of lanatoside C and were observed for a period of from two to thirty-four months following the institution of this study. The average time of observation was eleven months. So far as we have been able to determine, there has not been a single recurrence of auricular flutter. As a rule the successfully treated members of this group were discharged from the hospital within one week after the restoration of normal rhythm.

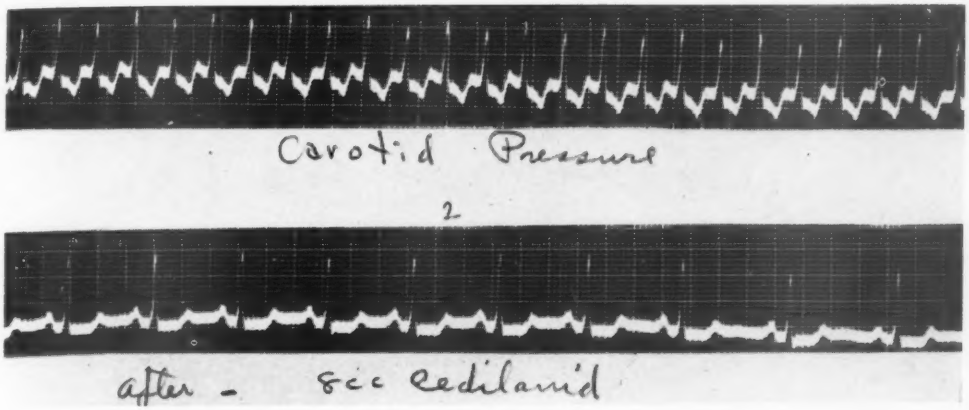
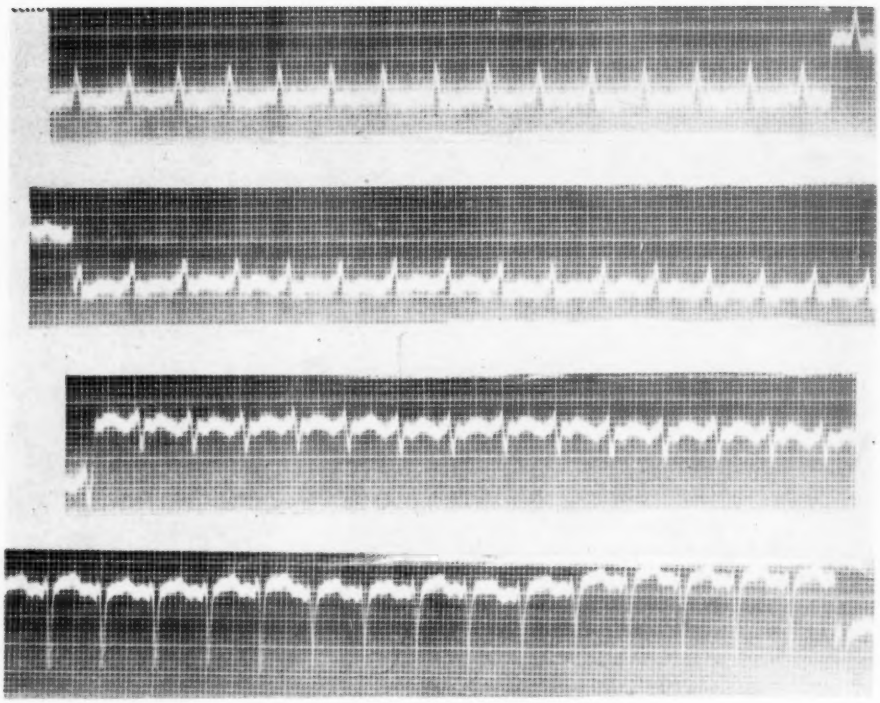


Fig. 3.—Case 2. Direct conversion of auricular flutter to sinus rhythm. Note: Carotid pressure was ineffectual. Sinus rhythm obtained in 50 minutes following 1.6 mg. of lanatoside C intravenously. Tracing taken in Lead II.

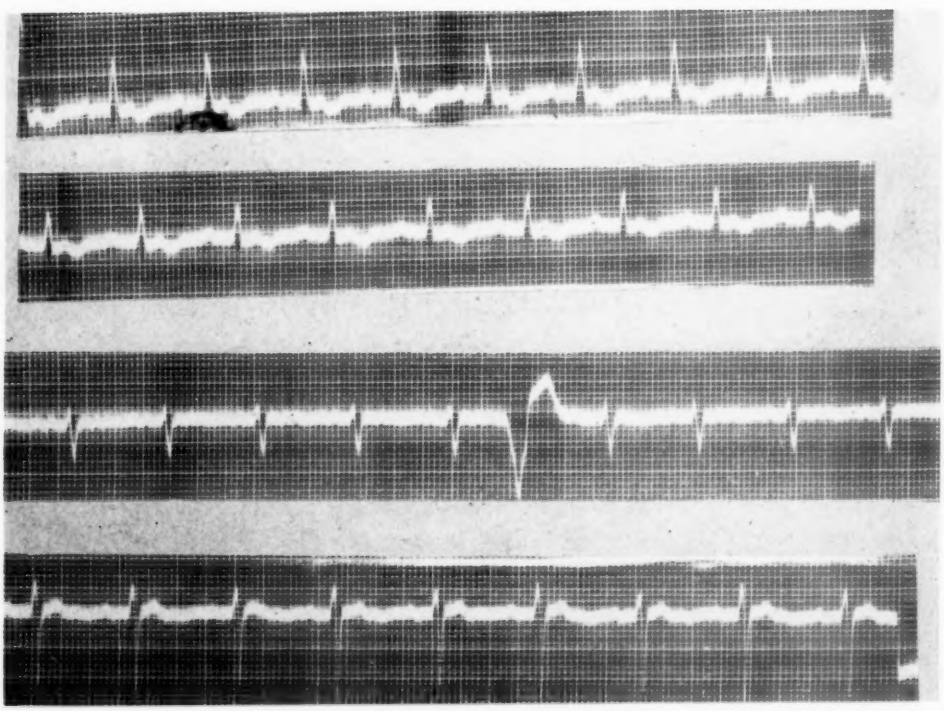
DISCUSSION

On the basis of historical and clinical evidence, we feel justified in classifying the auricular flutter in this group of patients as established. Many of the patients had failed to respond to varied therapeutic procedures, including quinidine and digitalis leaf alone and in combination. After reviewing the literature and considering our own experience, we feel that quinidine has no place in the initial therapy of auricular flutter. There are sound pharmacologic reasons for its failure. Digitalis, on the other hand, may be initially effective in the conversion of this arrhythmia to sinus rhythm or auricular fibrillation, especially if it be given intravenously in full dosage as the glycoside lanatoside C. Digitalis leaf frequently fails to convert this arrhythmia, and, when it does, this conversion is invariably very slow in occurring. Lanatoside C, due to its rapidity of action and strong vagal effect, has been shown to possess superiority over digitalis leaf in the treatment of established auricular flutter. This action is further fortified by follow-up maintenance therapy with the same drug. In patients whose auricular flutter was successfully converted to auricular fibrillation, the time for the conversion varied from two to seventy-two hours; in one patient the conversion did not occur until thirteen days after the initial medication. Serial electrocardiograms made at frequent intervals during the transition from auricular flutter to auricular fibrillation were exceedingly valuable therapeutic guides. We found that adequate medication should be maintained until conversion is complete. Utmost patience should be combined with careful clinical observation throughout the conversion period, particularly when complicating disease is present, as it was in four patients of our series. The presence of associated disease unquestionably prolonged the conversion period.

Little attention has been given to the primary slowing of the ventricular rate which occurs when lanatoside C and other forms of digitalis are given in auricular flutter. This slowing effect designates an increase in A-V block, and

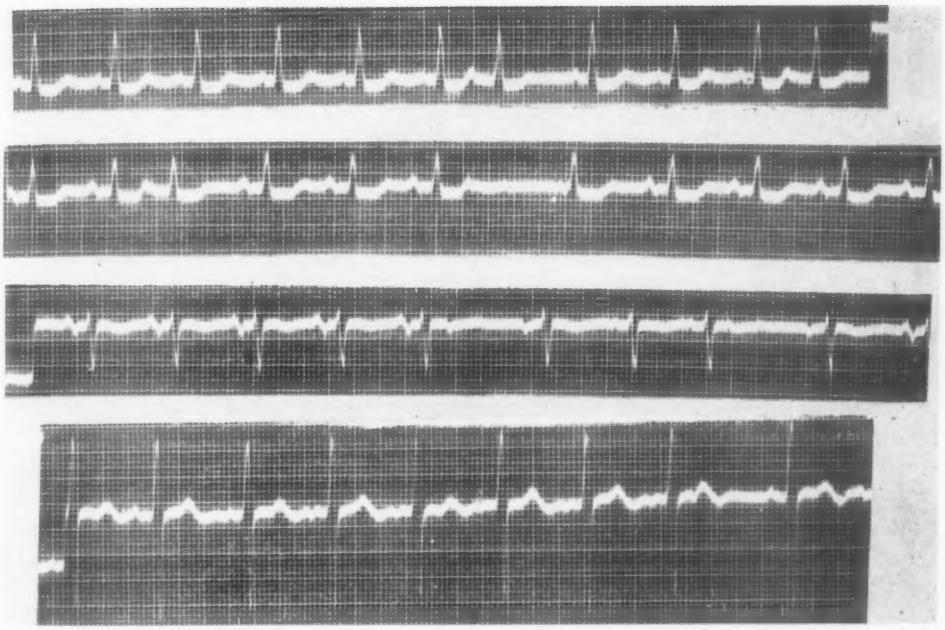


A.



B.

Fig. 4.—*For complete legend, see opposite page.*



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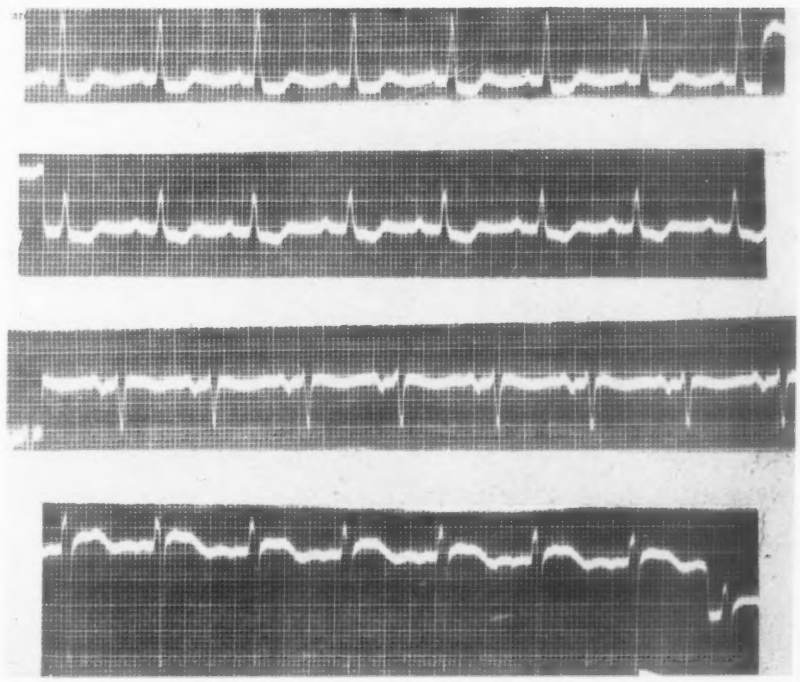

D.

Fig. 4.—Case 13. Direct conversion of auricular flutter to sinus rhythm with 1.6 mg. of lanatoside C intravenously. *A*, Auricular flutter with a ventricular rate of 150 per minute. *B*, Two hours later demonstrating slowing effect and increased A-V block. *C*, Twenty-four hours after lanatoside C establishment of sinus rhythm. Note: Occasional auricular premature contractions were present. *D*, Three days later. Patient receiving 1 mg. lanatoside C daily.

this block usually precedes the appearance of auricular fibrillation. We wish to emphasize the necessity of continued lanatoside C therapy in maintenance dosage until auricular fibrillation makes its appearance.

It is difficult to explain the mechanism of the direct conversion of auricular flutter into a sinus rhythm. This occurred in four of our patients. We feel that this conversion might have occurred spontaneously in due time without the aid of medication.

The effect of quinidine in the presence of auricular fibrillation is well known; if this drug is given according to individual requirements, satisfactory clinical effectiveness can be expected. In this study the time necessary for the conversion of auricular fibrillation into sinus rhythm by the use of quinidine varied from twelve hours to ten days.

When sustained auricular flutter requires both lanatoside C and quinidine in sequence to produce sinus rhythm, it seems plausible to assume that the conversion would not have occurred spontaneously. The use of these drugs, therefore, appears to be of value in the treatment of auricular flutter.

SUMMARY AND CONCLUSIONS

1. Lanatoside C and quinidine sulfate used in proper sequence are valuable drugs for the conversion of established auricular flutter into normal sinus rhythm.

2. Lanatoside C in full digitalizing dosage (1.6 mg.) followed by maintenance dosage (1 to 2 mg. daily) frequently converts auricular flutter to auricular fibrillation, and less frequently to sinus rhythm.

3. Following the administration of this drug, a primary slowing of the ventricular rate occurs which, in the main, is due to increased A-V block. This slowing usually precedes the conversion of auricular flutter to auricular fibrillation.

4. Except in the direct conversion of auricular flutter to sinus rhythm, the action of lanatoside C can be readily understood.

5. The action of quinidine in the presence of auricular fibrillation is quite dependable and well known.

6. Following the conversion of auricular flutter to auricular fibrillation by lanatoside C, the use of quinidine has proved of especial value in this study.

7. Conversion of established auricular flutter to sinus rhythm can be accomplished in the presence of diversified pathology.

8. Maintenance dosage of lanatoside C has proved of value as prophylactic therapy following the restoration of normal sinus rhythm.

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ELECTROCARDIOGRAPHIC CHANGES OCCURRING DURING TREATMENT WITH FUADIN SOLUTION

S. B. Beaser, M.D.,* and R. Rodriguez-Molina, M.D.†

CLINICAL medicine recognizes heart disease as one of the commonest causes for sudden death. In any condition, therefore, in which sudden death occurs, a cardiac origin should be suspected; moreover, evidence for unsuspected cardiac dysfunction in nonfatal cases of that disorder should be sought for. One such disorder is the toxicity due to antimony therapy of schistosomiasis.[1-3] Mainzer and Krause,[1] after observing such a fatality, performed electrocardiograms routinely on twelve patients receiving intravenous tartar emetic and found abnormalities in eight of them, all of whom were asymptomatic. The accidental finding of similar electrocardiographic changes in a patient receiving the reputedly less toxic fuadin (sodium antimony pyrocatechin) led to the present systematic electrocardiographic study of twenty-five patients under treatment for schistosomiasis with that drug.

PLAN OF STUDY

All twenty-five patients were Puerto Rican soldiers with schistosomiasis (Mansoni) who were receiving a uniform course of fuadin therapy. Electrocardiograms‡ were taken before and during treatment (Table I). The usual limb leads and CF_4 were taken with the patient in the same position and with standardizations recorded no sooner than two and one-half hours after meals[4] and one hour after the fuadin injections. Additional electrocardiograms were taken just after the tenth injection on certain positive cases as follows: two in inspiration and expiration both in the recumbent and upright positions; one fifteen minutes after the intravenous injection of 1/50 gr. of atropine dissolved in 10 c.c. of distilled water; one with bilateral carotid sinus pressure. In fourteen of the twenty patients who showed electrocardiographic changes, twenty-two follow-up electrocardiograms were performed during the three weeks after cessation of therapy.

The tracings were analyzed for all the common factors. The P-R interval was used as the basis for the isoelectric line and five successive complexes were averaged for each measurement. Following the criteria of Larsen and coworkers,[5] the outer limit of normal variation of the amplitude of T waves was con-

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*Assistant in Medicine, Harvard Medical School, and Head of The Diabetic Clinic, Beth Israel Hospital, Boston, Mass. (on leave of absence in the United States Army).

†Assistant Professor of Tropical Medicine, School of Tropical Medicine, San Juan, Puerto Rico, and Columbia University, New York, N. Y. (on leave of absence in the United States Army).

‡The General Electric Electrocardiograph (Model B) was used throughout.

TABLE I. FUADIN* THERAPY (DOSAGE SCHEDULE)

Day of treatment	0	1	2	3	5	7	9	11	13	15	17
Number of fuadin injections	0	1	2	3	4	5	6	7	8	9	10
Dose of fuadin in cubic centimeters	0	1.5	3.5	5	5	5	5	5	5	5	5
Accumulated dose of fuadin In cubic centimeters	0	1.5	5	10	15	20	25	30	35	40	45
In milligrams	0			0.63				1.89			2.84
Accumulated dose of antimony in milligrams	0			0.085				0.255			0.383
ECG performed	Control ECG			ECG				ECG			ECG

*Each cubic centimeter of fuadin solution contains 0.063 Gm. of fuadin and 0.0085 mg. of trivalent antimony.

sidered to be 0.1 mv, and definite changes had to persist for at least two tracings in order to be regarded as significant. Certain cases were considered to show no change, even though the T waves had a definite tendency to decrease in voltage (six in all), since they did not conform to the foregoing criteria. The ventricular gradient was measured* in one instance (Leads I and II of A and D of Fig. 2) according to the method of Wilson and co-workers.[6]

RESULTS

Significant changes from the normal were noted only in the T waves and S-T segments (Table II and Figs. 1-6). The analysis which included all important elements of the tracings showed no significant QRS, Q-T, or rate changes. Of the total of twenty-five patients, twenty, or 80 per cent, showed significant decrease in the height of the T waves in two or more leads. The amplitude of the T waves decreased therefore in fifty-nine of a total of 100 T waves. Seven patients developed T-wave changes in all four leads. In two (Figs. 2 and 4), T_4 had a cove-plane configuration.[16] The regression of the abnormal changes of forty-one T waves in fourteen patients was studied in detail in terms of the percentile return toward the pretreatment normal value of each T wave in the three weeks following cessation of treatment (Table III). These values can be considered only as estimates of the speed of recovery. Changes in position, inspiration and expiration, atropine, and carotid sinus pressure did not significantly alter the T-wave changes noted previously. The ventricular gradient showed a counterclockwise rotation to the left and a decrease in magnitude (Table IV and Fig. 7).

*We are indebted to Dr. A. Stone Freedberg for this analysis.

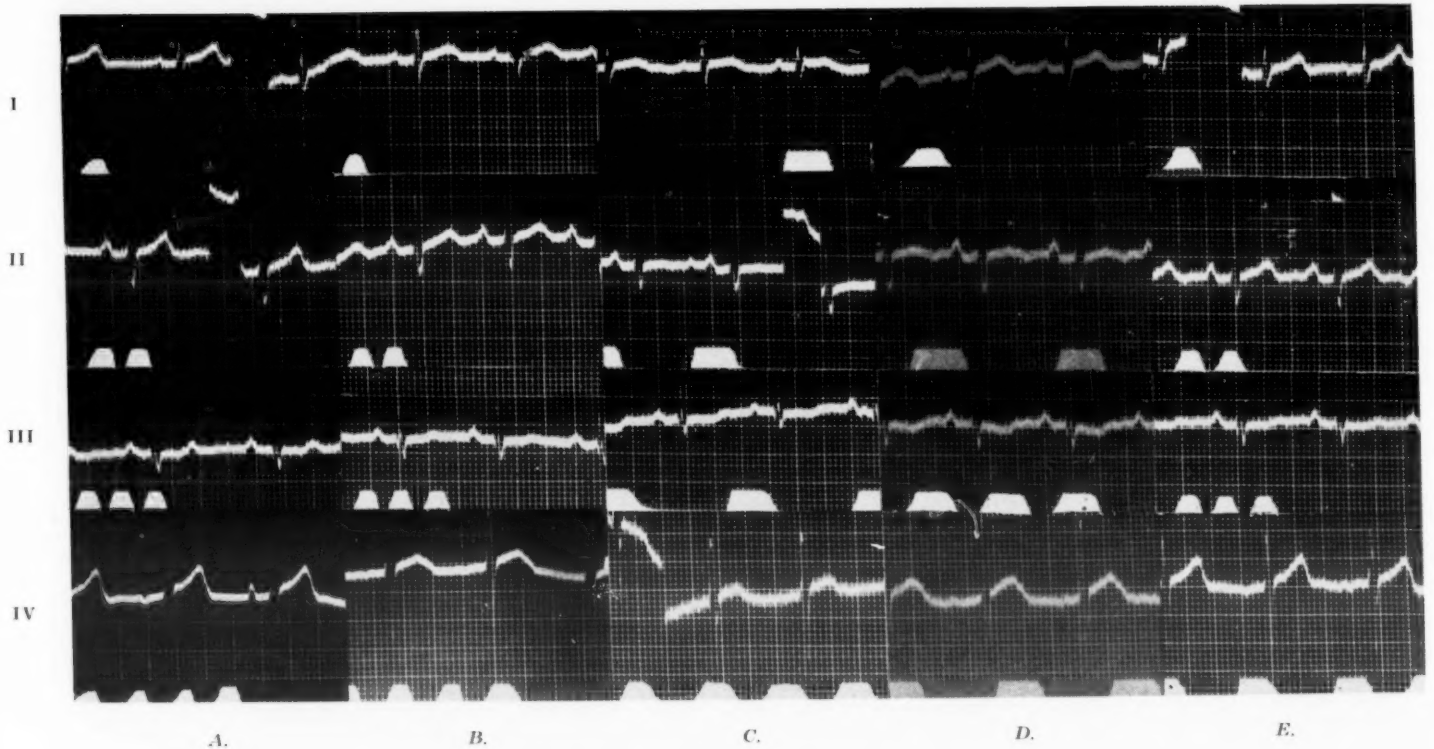

Fig. 1.—Case 1. *A*, Control; *B* and *C*, injections 7 and 10, respectively; *D* and *E*, four and eleven days, respectively, after *C*.

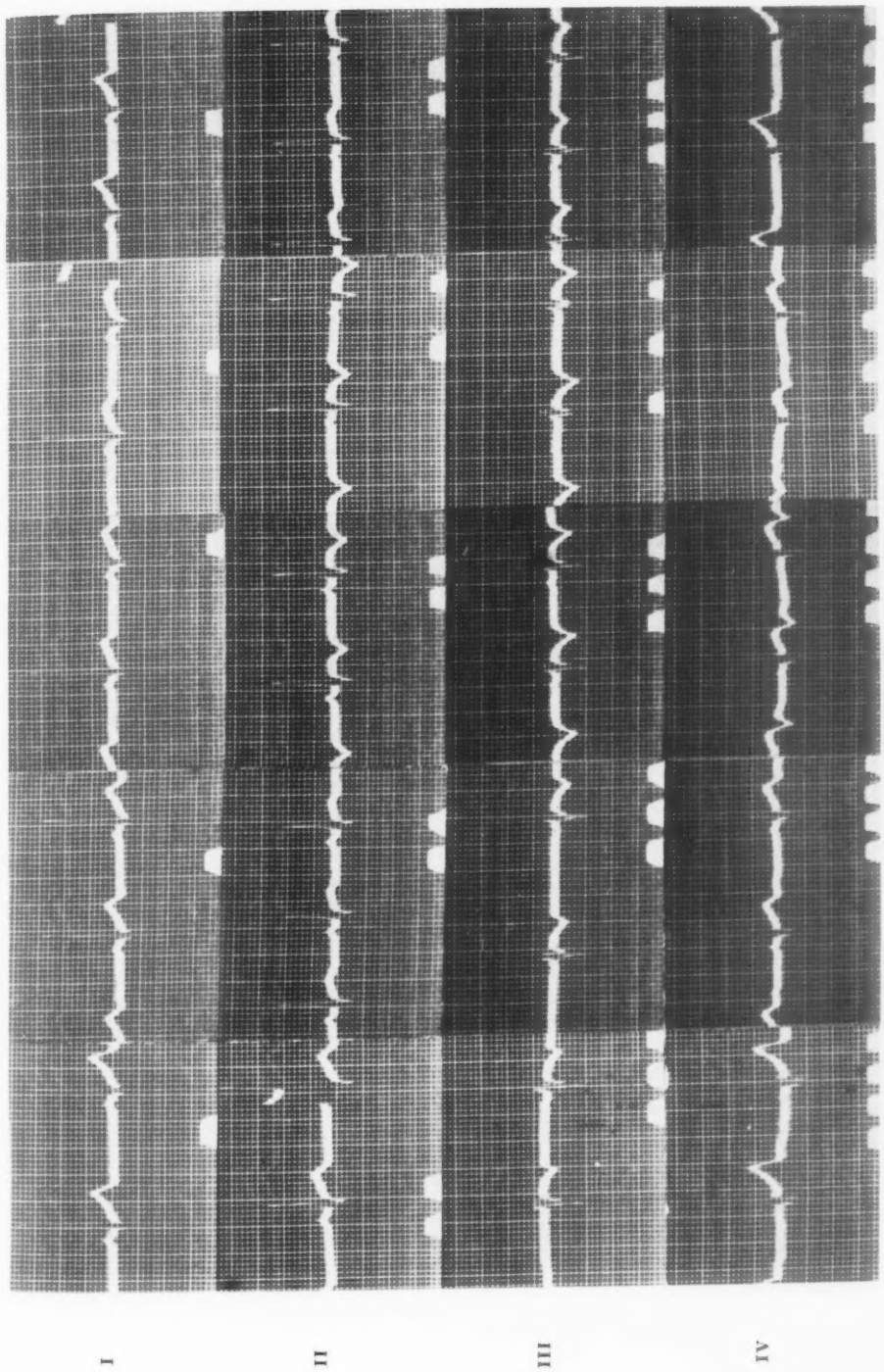

Fig. 2.—Case 5. *A*, Control; *B*, *C*, and *D*, injections 3, 7, and 10, respectively; *E*, seventeen days after *D*.

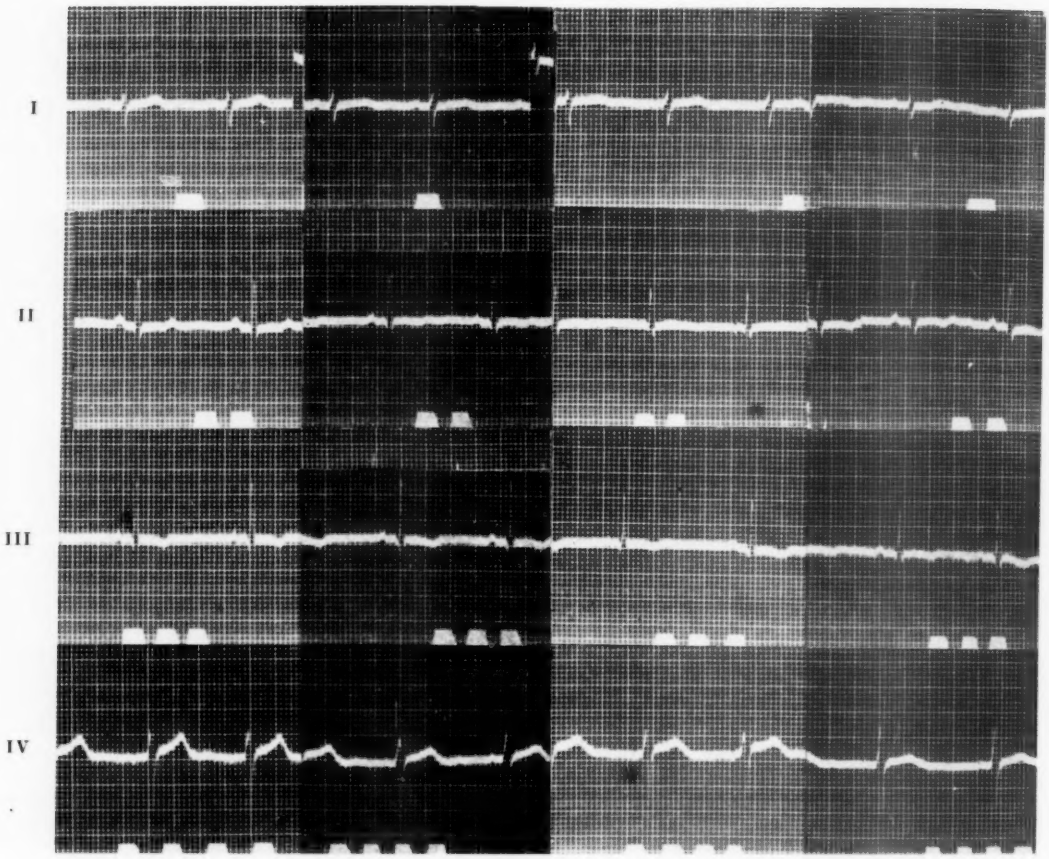

Fig. 3.—Case 6. *A*, Control; *B* and *C*, injections 7 and 10, respectively; *D*, three days after *C*.

TABLE II. ANALYSIS OF THE T-WAVE CHANGES OCCURRING DURING FUADIN THERAPY

	NUMBER OF PATIENTS DEVELOPING T-WAVE CHANGES	NUMBER OF PATIENTS DEVELOPING T-WAVE CHANGES AT INJECTION NUMBER			NUMBER OF PATIENTS WITH MAXIMUM CHANGE AT INJECTION NUMBER		
		3	7	10	3	7	10
T_1	14	6	5	3	1	2	11
T_2	19	14	5	0	0	2	17
T_3	8	1	4	3	1	2	5
T_4	18	14	2	2	3	4	12
Total							
Number	59	35	16	8	4	10	45
Per cent	100	60	27	13	7	17	76

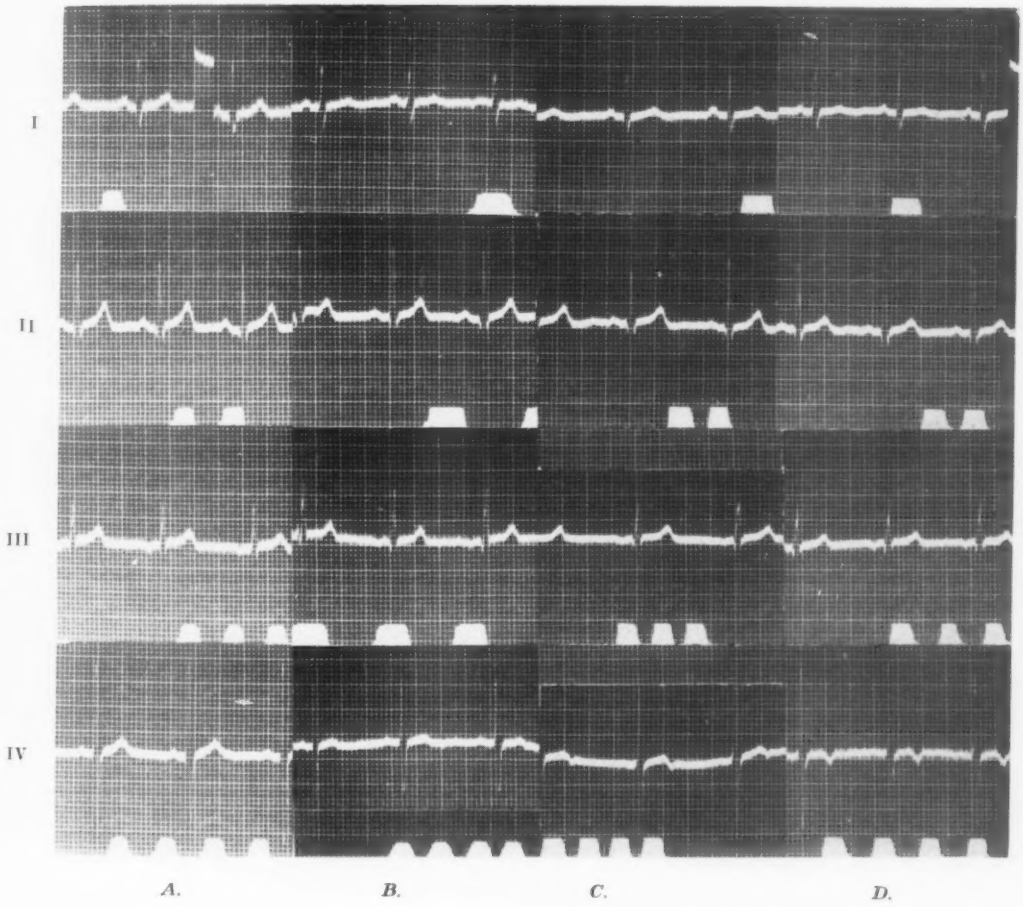

Fig. 4.—Case 17. *A*, Control; *B*, *C*, and *D*, injections 3, 7, and 10, respectively.

TABLE III. REGRESSION OF T-WAVE CHANGES AFTER CESSATION OF FUADIN THERAPY

	NUMBER OF DAYS AFTER LAST INJECTION		
	0 to 7	8 to 15	16 to 22
Total number cases studied	11	8	3
Average return to normal height of T waves in per cent	33	63	73

TABLE IV. MEASUREMENT OF VENTRICULAR GRADIENT OF CASE 5 (FIG. 2)

FACTOR	CONTROL (A)	AFTER FUADIN (D)
QRS_1	+34.0 m. v. s.	+23.5 m. v. s.
T_1	+59.0 m. v. s.	+16.0 m. v. s.
QRS_2	+17.0 m. v. s.	+16.0 m. v. s.
T_2	+31.0 m. v. s.	−28.0 m. v. s.
$\hat{A}_{QRS}$	35.5 m. v. s. −1°	24.0 m. v. s. +13°
$\hat{A}_T$	59.0 m. v. s. +1°	46.0 m. v. s. −68°
$\hat{A}_{QRST}$	95.0 m. v. s. 0°	54 m. v. s. −44°

DISCUSSION

Antimony has been shown to have no immediate effect upon the electrocardiogram of the dog[9] but does cause weakening of the heartbeat with cardiac dilatation both in dogs[9] and frogs.[10,11] In more prolonged toxicity experiments in dogs, this drug has been shown to accumulate chemically much less in the heart than in the lungs, liver, and kidneys.[12,13] Likewise, pathologic changes in the liver and kidneys preceded heart involvement in the dog. Severe symptoms of hepatic and renal damage were evident at a time when the contrastingly mild heart damage was clinically not evident (electrocardiograms were not taken in these experiments).

In man, the toxic symptoms after antimony treatment consist of vomiting, collapse, fever, and muscular pains. These occur in only 1 per cent of patients receiving fuadin (less than after tartar emetic). The reasons for the variation in individual susceptibility are unknown, but the excretion of fuadin has been noted to vary from person to person, with a noticeable delay in those with renal excretory difficulty. Mainzer and Krause,[1] in their electrocardiographic study of patients under tartar emetic therapy, noted that the heart rate decreased slightly,* that the T waves became flat or inverted, and that the S-T and T elements became "indistinctly separated and fused with one another." They found that the changes occurred early (usually in the second tracing) after 0.72 to 1.08 Gm. of tartar emetic, but they did not determine the recovery rate by following their cases. Magalhães and Dias[15] found similar T-wave changes in twenty-one patients receiving antimony therapy. These changes were present in seven of fourteen of their recorded electrocardiograms. Of these, one-half the patients had received tartar emetic, but it was not clear which antimony compounds the remaining patients had received. After completion of these studies, Tarr[16] published a preliminary report showing that twelve of thirty-eight patients receiving intravenous tartar emetic and two of twenty-eight patients receiving intramuscular fuadin showed significant electrocardiographic changes consisting of decrease in the voltage of the T waves.

*The bradycardia has been shown to be a vagus effect.

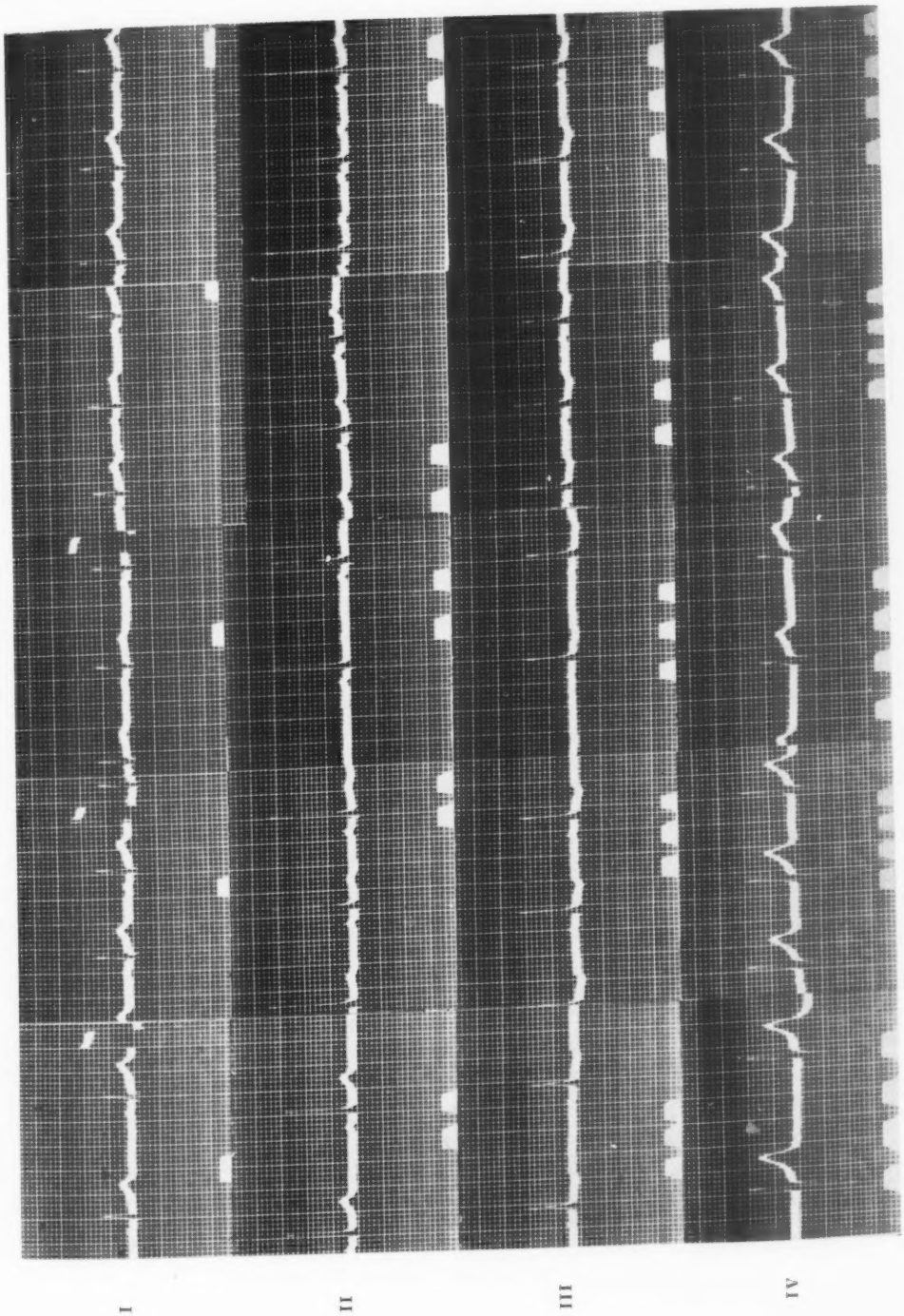

Fig. 5.—Case 24. *A*, Control; *B* and *C*, injections 3 and 10, respectively; *D* and *E*, seven and fifteen days, respectively, after *C*.

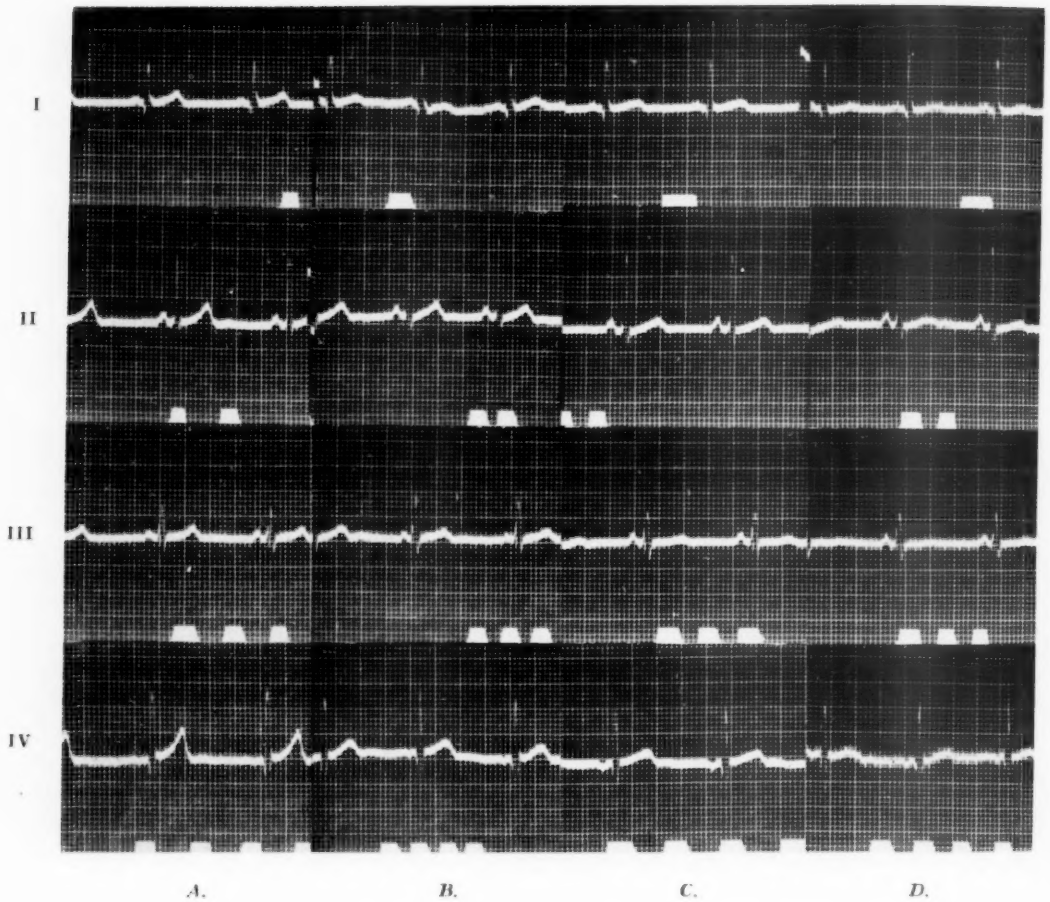

Fig. 6.—Case 25. *A*, Control; *B* and *C*, injections 3 and 10, respectively; *D*, seven days after C.

The mechanism of the fuadin effect is unknown, but it seems to be definitely reversible. Digitalis, which also has a reversible action upon the myocardium, affects chiefly the magnitude of the ventricular gradient (decrease). A shift in direction of the ventricular gradient has also been noted in myocardial ischemia.[17] This is of interest since Magalhães and Dias[15] ascribed the effects of antimony "to dilatation of the capillaries or the coronary circulation with diminution in the effective circulation to the heart."

Of more than theoretical interest is the similarity of the changes seen after administration of fuadin and those observed in patients with intercurrent infection[18] or phosphorus poisoning[19] who have been shown to develop similar unsuspected and asymptomatic T-wave changes and who may die suddenly with pathologically demonstrated myocardial changes. Practically, the facts warrant

the clinical precaution that the frequently repeated courses of fuadin be spaced four or more weeks apart to avoid a cumulative effect upon the myocardium, even though that effect is probably reversible in nature.

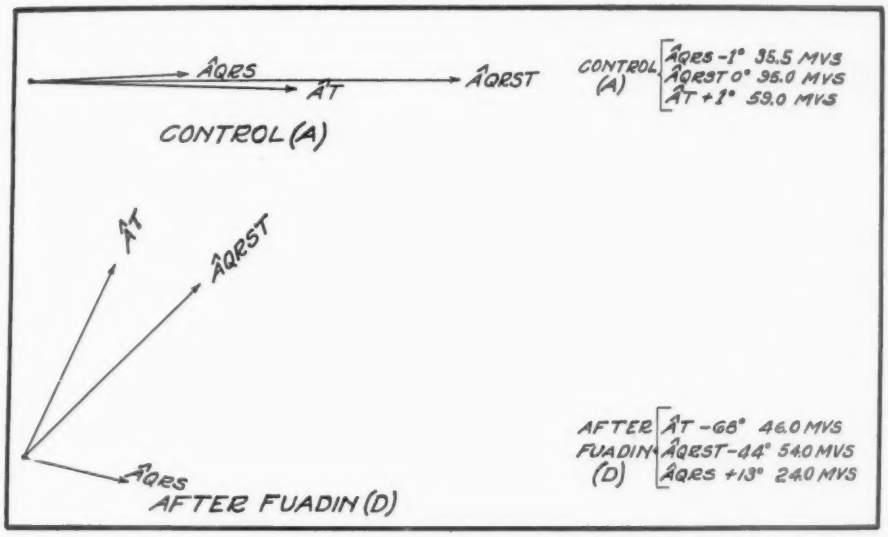

Fig. 7.—Case 5. Ventricular gradient before and after fuadin (Fig. 2, *A* and *D*, respectively).

SUMMARY

1. Of twenty-five patients receiving a course of fuadin therapy for schistosomiasis, twenty showed decrease in voltage of the T waves of the electrocardiogram.

2. These changes occurred early (60 per cent after the third injection) and were reversible, regressing in three or more weeks.

3. The ventricular gradient in one patient was analyzed and showed a definite shift in direction.

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ORTHOSTATIC PAROXYSMAL VENTRICULAR TACHYCARDIA

CAPTAIN MICHAEL PETERS, M.C. AND CAPTAIN SIDNEY L. PENNER, M.C.
ARMY OF THE UNITED STATES

IN THE course of observations on the effect of changes in posture and various drugs on the cardiovascular system, we encountered an instance of orthostatic paroxysmal ventricular tachycardia. We believe this finding is unusual enough to warrant reporting.

REPORT OF CASE

Mrs. H. H., aged 24 years, was first seen in June, 1945, complaining of attacks of rapid heart action occurring since January, 1944. Each of these attacks began with a sensation of "pressure against the heart and gas in the stomach." The heart would then begin to beat rapidly, stop for a few beats, and then beat fast again. This was accompanied by a stuffy feeling in the ears and a sensation of blood rushing to the head. However, the attacks never occurred while the patient was lying down but appeared only in the upright position, and in this position were precipitated by excitement or mild exertion. From January, 1944, to June, 1944, attacks of rapid heart action occurred about once a month. In June, 1944, she became pregnant. The attacks were unchanged for the first five months of pregnancy, but did not recur during the remainder of the pregnancy nor during a rather difficult three-day labor. However, two weeks after delivery, she had an identical episode on getting out of bed for the first time and since then the attacks have occurred once or twice weekly. In the free intervals she has enjoyed excellent health except for "some nervousness." She has never had any dyspnea or edema. Past history included measles, mumps, chicken pox, and whooping cough in early childhood without known sequelae. There was no history of diptheria, scarlet fever, or rheumatic fever in any of its varied manifestations. She did not use alcohol, coffee, tobacco, or any medication.

The physical examination was entirely normal. The blood pressure was 110/60. The blood count, urinalysis, and blood Kahn were normal. The basal metabolic rate was −4 per cent. X-ray examination of the heart in the posteroanterior and left lateral positions with barium in the esophagus was normal. The lung fields were clear.

Two weeks after the original consultation, the patient was seen during a spontaneous attack of tachycardia. At this time the apex and pulse rates were 150 to 180 per minute and were irregular. There were runs of rapid regular rhythm interrupted frequently by a slower rhythm. She was apprehensive and tremulous but not in acute distress.

An electrocardiogram was taken in the supine position. Leads I, II, III, and CF_2 showed brief runs of ventricular tachycardia, interrupted by one or two sinus beats. Lead CF_4 showed a normal sinus rhythm. This change to regular rhythm did not surprise the patient, who pointed out that she could always stop an attack by lying down but that the tachycardia would recur upon resuming the upright position. An electrocardiogram was therefore taken in the upright position; this record showed ventricular tachycardia once again.

On July 1, 1945, the patient stated that she had had three attacks in the preceding two weeks. Examination showed a regular sinus rhythm. After fifteen hops on each foot, she developed an attack of ventricular tachycardia proved by an electrocardiogram. Ergotamine

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tartrate, 0.5 mg., was given intravenously while the patient was in the standing position. She complained of feeling weak and sat down. An electrocardiogram in this position still showed ventricular tachycardia, but twenty-five minutes later the electrocardiogram showed normal sinus rhythm. When she stood up, the tachycardia did not recur, and the next day she reported no recurrence of the attacks. She was then advised to take 0.3 Gm. of quinidine sulfate daily. On July 10, 1945, she reported, by phone, that she had not had any further attacks. Unfortunately, she was lost to our further observation after this date.

DISCUSSION

The diagnosis of ventricular tachycardia depends primarily on electrocardiographic findings although it can be suspected clinically. It has been shown[1] that the rhythm is not absolutely regular. Minor variations in the length of the cardiac cycle occur which can be detected by careful auscultation. In addition, there are variations in the intensity of the first heart sounds which are due to the changing time relations between auricular and ventricular systole. Close observation may also reveal *a* waves in the jugular pulse which are slower in rate than the apex beat. Further, vagal stimulation does not influence the heart rate in ventricular tachycardia as it does in paroxysmal auricular tachycardia and in auricular flutter. If auricular fibrillation is known to have existed, the sudden development of a marked rise and fall in the apex rate would suggest ventricular tachycardia, especially after heavy digitalization.[2]

Although ventricular tachycardia had been recognized as early as 1909,[3] the criteria for the electrocardiographic diagnosis were first cyrstallized by Robinson and Herrmann in 1921.[4] As amended by Cooke and White,[2] they include:

1. The identification of P waves during the paroxysm at a slower rate than the QRS complexes.
2. A paroxysm of abnormal ventricular complexes, i. e., three or more at a rapid rate, occurring during auricular fibrillation.
3. The onset of tachycardia with an abnormal ventricular complex.
4. A close resemblance, in the same lead, of the QRS complexes of the ventricular premature beats to the QRS complexes occurring during the tachycardia.

Only one of these conditions is needed to establish the diagnosis of paroxysmal ventricular tachycardia. The present case illustrates 3 and 4 of the criteria just given (Figs. 1 and 2). We were unable to identify P waves during the paroxysm.

Clinical Features.—Ventricular tachycardia is not a common arrhythmia. Cooke and White[2] found the disturbance only twenty-four times in a study of the records of 25,000 patients. Most articles on this subject report isolated cases; the largest personal series comprised thirty-six cases,[5] while Cooke and White reported twenty-seven cases.[2]

Paroxysmal ventricular tachycardia is usually due to serious organic heart disease, especially coronary artery disease, but may develop after the administra-

tion of digitalis,[6] epinephrine,[7, 8] or related drugs.[9] It may also be induced in presumably normal hearts by chloroform[10] and similar compounds.[11] In addition, a limited number of instances of paroxysmal ventricular tachycardia has been reported in relatively young persons with normal hearts and no external precipitating causes.[2, 8, 12-18] Follow-up on some of these patients was continued for as long as fourteen years without developing any signs of heart disease.

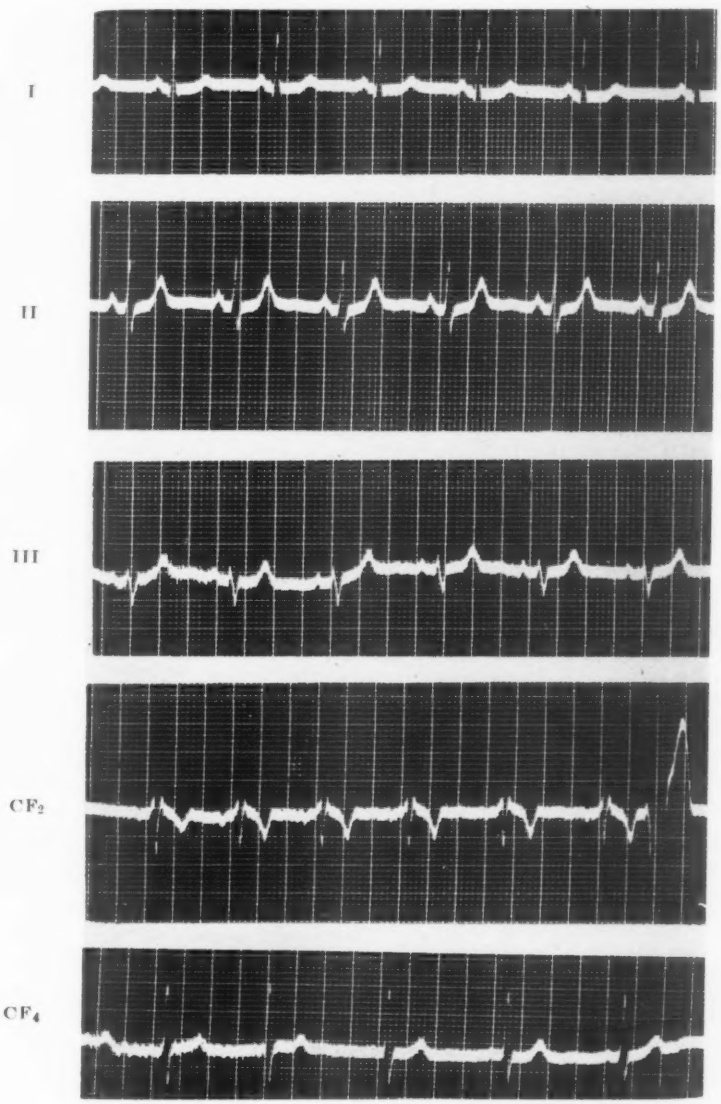

Fig. 1.—An electrocardiogram made with the patient in the supine position. The mechanism is normal.

The symptoms associated with ventricular tachycardia vary considerably, depending on the heart rate, the duration of the paroxysm, the degree and type of heart disease present, as well as the coexistence of extracardiac pathologic states. Although some subjects have no symptoms and may be unaware of the

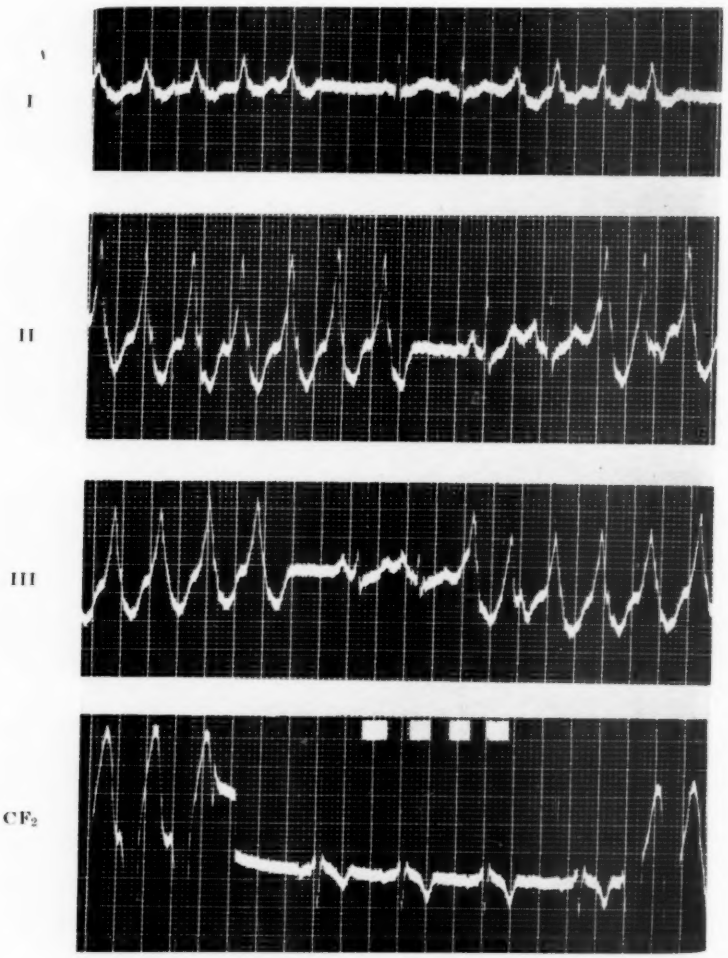

Fig. 2.—An electrocardiogram made with the patient erect shows runs of ventricular paroxysmal tachycardia interrupted by a few normal cycles.

arrhythmia, most patients complain of palpitation, precordial fluttering, or weakness. In some instances the rapid heart rate may be associated with a diminished cardiac output[19,20] resulting in dizziness and syncope.[11,18,22] When the ventricular rate is rapid and the paroxysm prolonged, heart failure may result, even in the absence of organic heart disease.[8] Anginal pain may be a conspicuous feature in patients with myocardial damage, though this need not be present.[21]

In many cases, such as the one presented here, psychogenic symptoms occur as a result of repeated attacks over a long period of time in an emotionally unstable individual.

The individual paroxysm of ventricular tachycardia usually begins with isolated ventricular premature beats, followed by short runs, which finally become continuous and replace the normal sinus rhythm. The physical findings during the paroxysm which would suggest to the clinician the nature of the arrhythmia have already been outlined, as have the electrocardiographic criteria.

The prognosis of ventricular tachycardia is properly regarded as ominous, due both to the arrhythmia itself and to the almost invariably co-existent heart disease. In a group of twenty-two patients with paroxysmal ventricular tachycardia and coexisting heart disease, twenty died within two years of the first attack.[2] Of fifty similar cases reported by Strauss,[23] forty died within six months of the onset, with an average duration of life of twenty-four days. However, the prognosis may be regarded as more favorable in patients with chronic heart disease, in the absence of acute cardiac damage,[24] or when appropriate therapy is employed early in the course of the paroxysm with a favorable response.[25,26]

In apparent contrast to this larger group of patients with organic heart disease is the limited group in whom no heart disease can be demonstrated on examination; this group appears to have a far more favorable prognosis. Cooke and White[2] have continued follow-up on such cases for as long as nine, twelve, and even fourteen years after the onset of paroxysms of ventricular tachycardia. However, even in this type of patient the arrhythmia carries hazards of its own, for there always remains the possibility of sudden death due, perhaps, to the development of ventricular fibrillation. Such cases have been repeatedly reported.[27,28] Further, the development of severe[8] or even fatal heart failure as the result of an uncontrollable attack has been recorded. With the more widespread use of appropriate therapy, including parenteral quinidine in adequate dosage,[29] this particular hazard may, at times, be averted. Specific criteria for a group of "benign" cases of paroxysmal ventricular tachycardia have been suggested.[15] They are (1) the youth of the patient; (2) the long follow-up; (3) clinically normal hearts; (4) normal electrocardiograms during regular sinus rhythm; and (5) nomorphism of the aberrant QRS complexes during the tachycardia. However, in view of the hazard inherent in this arrhythmia, it is believed that the appellation of "benign" is inappropriate.

Physiologic Considerations.—It has long been known that sympathetic stimuli can cause ventricular tachycardia. Hoff and Nahum[30] were able to produce ventricular rhythms by administering adrenalin and, conversely, found that benzol poisoning, which regularly produced ventricular tachycardia, was ineffectual in the absence of the adrenal glands. Kirk and Kilpatrick[7] reported a patient with coronary artery occlusion in whom adrenalin produced ventricular tachycardia, while Herrmann[9] reported a similar experience with ephedrine. Furthermore, mecholyl, a parasympathomimetic drug, was found to abolish the arrhythmia in animals,[30] while atropine, a parasympatholytic drug, induced a paroxysm in Scott's patient.[8]

It is also recognized that the sympathetic nervous system plays an important part in the vascular adjustments taking place in man on assuming the upright position. The intitial transient drop in blood pressure of 5 to 40 mm. Hg stimulates receptors in the carotid sinus, aortic arch, mesentery, and perhaps elsewhere to raise the pulse rate and bring about vasoconstriction in both the splanchnic and peripheral areas.[31] These compensatory mechanisms are mediated by the sympathetic nervous system. In some individuals, the adjustments are inadequate and result in orthostatic hypotension,[32] while in others, evidences of excessive sympathetic activity can be found. Thus, Wendkos[38] has reported T-wave changes in the electrocardiogram which appear on assuming the upright position and can be abolished by administering a sympatholytic drug. Comparable postural effects on the P-R interval have also been noted.[35,36]

In the present case there was a clear-cut relation of the paroxysms of ventricular tachycardia to posture, noted both in the history and on clinical observation. Attacks occurred only in the upright position. They could always be terminated by lying down, only to recur upon reassuming the upright position. Further, the attacks could be readily precipitated by exertion or excitement, factors which are known to be associated with increased sympathetic tone.[37] In several case reports of "benign" ventricular tachycardia, one finds notations that the attacks were precipitated by exertion,[8,14,27] while in one of these cases[8] it was noted that the paroxysms were occasionally relieved by the supine position, resembling our case in this respect. A similar experience in two cases of auricular tachycardia has been reported.[34] It is interesting to note that our patient had no attacks in the last trimester of pregnancy, at a time when increased intra-abdominal pressure and increased blood volume would tend to minimize the reflexes ordinarily active on assuming the upright position.

These considerations, therefore, made it appear likely to us that the attacks of paroxysmal ventricular tachycardia were due to unusually strong sympathetic tone produced by assuming the upright position, by exertion, or by excitement. With this thought in view, the patient was given an intravenous injection of 0.5 mg. of ergotamine tartrate during a paroxysm. Within twenty-five minutes the attack ceased and could not be reporduced thirty minutes later by the assumption of the upright position. Since the pharmacologic action of ergotamine in this dosage is sympatholytic,[33] the result obtained would support the view that autonomic imbalance is the cause of the tachycardia. Unfortunately, we did not have an opportunity to try mecholyl which was used in animals by Hoff and Nahum.[30] Pertinent to this problem is Scott's observation that atropine, a parasympatholytic drug, induced a paroxysm of ventricular tachycardia in his patient. Had a parasympathomimetic drug been used effectively in our case, the role of the autonomic nervous system in the causation of this arrhythmia related to posture would have been strengthened. The fact that mecholyl was used unsuccessfully in the unusual case recently reported by Chapman[39] does not invalidate these conclusions.

SUMMARY

An unusual instance of orthostatic paroxysmal ventricular tachycardia in a young woman with no other evidence of heart disease is reported. The relation to autonomic imbalance is discussed.

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Clinical Reports

ANEURYSM OF THE DESCENDING THORACIC AORTA

SAMUEL A. LOEWENBERG, M.D., and SAMUEL BAER, M.D.
PHILADELPHIA, PA.

BECAUSE of the comparative rarity of aneuyrsms of the lower thoracic aorta and because the diagnosis is frequently missed, we feel justified in discussing this condition and reporting such a case. Most reported series of aortic aneurysms are divided into three groups; that is, those of the arch, of the thoracic aorta, and of the abdominal aorta. Of these, aneurysms of the descending thoracic aorta are the least common.

Lucke and Rea,[1] in their series of 321 aortic aneurysms, found that 173 were in the arch, 40 in the abdominal, and 31, or 11.7 per cent, in the thoracic aorta. Of these, the number of lower thoracic aneurysms were found to be comparatively few. Brindley and Schwab[2] stated that 2 per cent of aortic aneurysms were found in the lower thoracic aorta, and Kampmeier[3] noted 30 of 633 aortic aneurysms (4.7 per cent) were in the descending thoracic aorta. Levitt and Levy[4] reported about the same incidence; of ninety-four aortic aneurysms, four were found in the descending thoracic aorta.

Not only are these aneurysms of the thoracic aorta rare, but, because of their location and because of the varied clinical pictures which they produce, they may frequently remain undiagnosed during life. Nonetheless, a review of the literature suggests that the clinical features and roentgen findings in most instances are sufficiently characteristic to warrant the diagnosis of aneurysm of the descending aorta.

CASE HISTORY

W. B., a colored man 61 years of age, complaining of abdominal pain, was admitted Feb. 11, 1944, to the Philadelphia General Hospital on the surgical service. The patient had been in his usual state of health until Jan. 23, 1944, when he first noted weakness and general malaise and a slight cough. A physician told him he had "flu" and recommended bed rest. About a week after the onset of the illness he began having abdominal pain. The pain was located in the upper abdomen just above the umbilicus. It was dull but persistent and was aggravated by coughing and deep breathing. The remainder of the present history was essentially negative. The previous history revealed that in 1941, upon admission for a suprapubic prostatectomy, a strongly positive Wassermann had been found.

The patient appeared quite comfortable. The temperature was 100.4° F.; the pulse rate, 100 per minute; the respiratory rate, 20 per minute; and the blood pressure, 120/80. The other

From the Medical Service of Dr. Samuel A. Loewenberg, Philadelphia General Hospital.
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significant findings were a few crackling râles in the right lower lung posteriorly and moderate tenderness bilaterally in the upper abdomen. A tentative diagnosis of influenza or subacute cholecystitis was made. On Feb. 12, 1944, a cholecystogram and a routine chest x-ray film were negative. In view of the absence of physical signs and of significant laboratory findings suggesting a surgical diagnosis, the patient was transferred to the medical service.

When first seen in the medical wards, the patient did not appear acutely ill. He continued to run a temperature fluctuating between 99 and 102° Fahrenheit. Physical examination revealed somewhat sluggish pupils, tremors of the hands, an impaired percussion note, and a few moist râles in the right upper lobe posteriorly. A diagnosis of subsiding pneumonitis of the right upper lobe was considered.

The Wassermann reaction was reported positive on two occasions. The interpretation of a second cholecystogram done March 1, 1944, was "nonvisualization of the gall bladder." The spinal fluid was found to be completely normal. Blood sugar and blood urea were normal, urine and blood cultures were sterile, and agglutination studies for typhoid, paratyphoid, and undulant fever were negative. A blood count revealed 3,000,000 erythrocytes and 13,400 leucocytes, of which 72 per cent were polymorphonuclear cells. A gastrointestinal series was begun March 14, 1944. Upon fluoroscopy and roentgen study of the esophagus and stomach, it was noted that the esophagus in its lower portion was displaced anteriorly and to the left by a mass lying anterior and to the right of the spine. Fluoroscopically this lesion appeared to be continuous with the descending aorta. X-ray examination of the spine showed suggestive evidence of erosion of the bodies of the ninth and tenth dorsal vertebrae on the right (Figs. 1, 2, and 3). Based on these findings a diagnosis of aneurysm of the descending aorta was made. Because of the unusual displacement of the esophagus, it was assumed that the aneurysm was located in the lower thoracic aorta as it entered the hiatus of the diaphragm.

The patient's condition became progressively worse. His cough became more severe and he expectorated bright red blood. The cough was present only in the morning and on one occasion was accompanied by the expectoration of a cupful of bright red blood. The temperature continued elevated, but with sedation the cough and hemoptysis subsided. On the morning of March 21, 1944, the patient was suddenly seized with a severe paroxysm of coughing with profuse hemoptysis and died before a physician could reach his bedside.

Autopsy.—Autopsy was performed four hours post mortem. The body was that of a well-developed, well-nourished, middle-aged Negro man. There was a suprapubic cystotomy scar. Slight axillary and inguinal lymphadenopathy was noted.

Approximately 250 c.c. of clear, straw-colored fluid were found in the right pleural cavity and about 100 c.c. in the left pleural cavity. There appeared to be approximately from 150 to 200 c.c. of pericardial fluid which was not well measured and about 750 c.c. of slightly opalescent fluid in the peritoneal cavity. There were a few adhesions between the gall bladder and the mesentery of the transverse colon. The peritoneal surfaces were otherwise smooth and glistening. The dome of the urinary bladder was adherent to the anterior abdominal wall beneath the site of the cystotomy wound. The aorta showed tree-bark wrinkling throughout and many atherosclerotic plaques. The mouths of the coronary arteries were widely patent. The ascending portion of the arch was somewhat dilated. At the lowermost portion of the descending aorta just above the diaphragm, a large saccular aneurysm was found. The ostium of the aneurysm measured 6 cm. in diameter and seemed completely filled with a thrombus. The thrombus and sac measured 10 cm. in diameter and extended into the left pleural cavity, pressing upon the left lower lobe. The pleura here was adherent to the aneurysmal sac which had ruptured into the lung tissue at the base of the sac. The heart appeared normal in size. The myocardium showed gross fibrosis. The aortic valve cusps were thin and mobile. The sinuses of Valsalva were somewhat stretched due to dilatation of the aorta. The mitral valve leaflets showed a few thickened areas. The coronary arteries had a minimal amount of sclerosis but appeared normal otherwise.

The left lung weighed 460 grams; the right, 500 grams. The lungs revealed smooth and glistening pleural surfaces, beneath which areas of hemorrhage could be seen. There was a fine

generalized emphysema which made the lungs pillowy to palpation. The sectioned surfaces showed the bronchi to be filled with blood which was clotted. The pulmonary tissue showed diffusely scattered blood-red areas due apparently to aspiration of blood in the alveoli. A probe passed through the bronchus of the right lower lobe entered the area at the base where the aneurysm had ruptured into the lung; this area was apparently the source of the blood in the bronchial tree. The pulmonary vessels were patent.

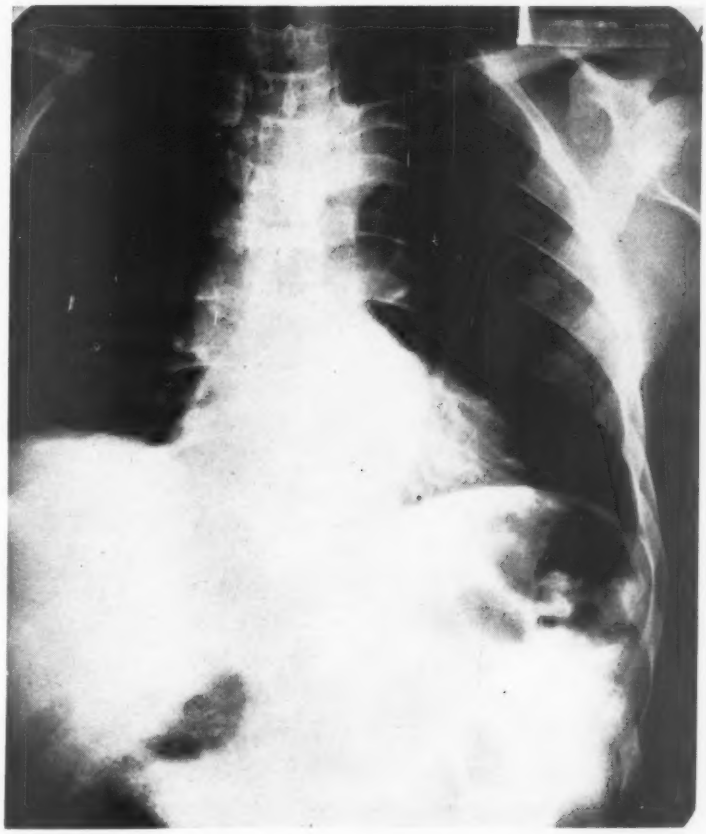

Fig. 1.—Note the shadow of the aortic aneurysm behind the cardiac silhouette.

The spleen weighed 80 grams and was normal in size. Its sectioned surface showed the follicular markings well against a blood-red pulp. The axillary, inguinal, and mesenteric lymph nodes were slightly enlarged and rubbery in consistency.

The left kidney weighed 190 grams; the right, 170 grams. The kidneys appeared normal in size. Their capsules stripped with slight difficulty to reveal a finely granular surface which retained some degree of fetal lobulation and also showed a few small, red, shallow, depressed scars. The sectioned surfaces showed congestion. The markings of the cortex and medulla appeared grossly normal in outline and ratio. The renal pelves were thickened. The ureters showed slight thickening of their walls. The right renal pelvis was subdivided and terminated in a double ureter which united at a point approximately located at the edge of the pelvic brim. The urinary

bladder was adherent to the anterior abdominal wall. There appeared to be a scar on the left side of the bladder fundus. The bladder mucosa was congested. The left testicle was one-half the size of the right, which appeared normal in size. There was a scar in the midline at the base of the bladder extending into the prostatic urethra.

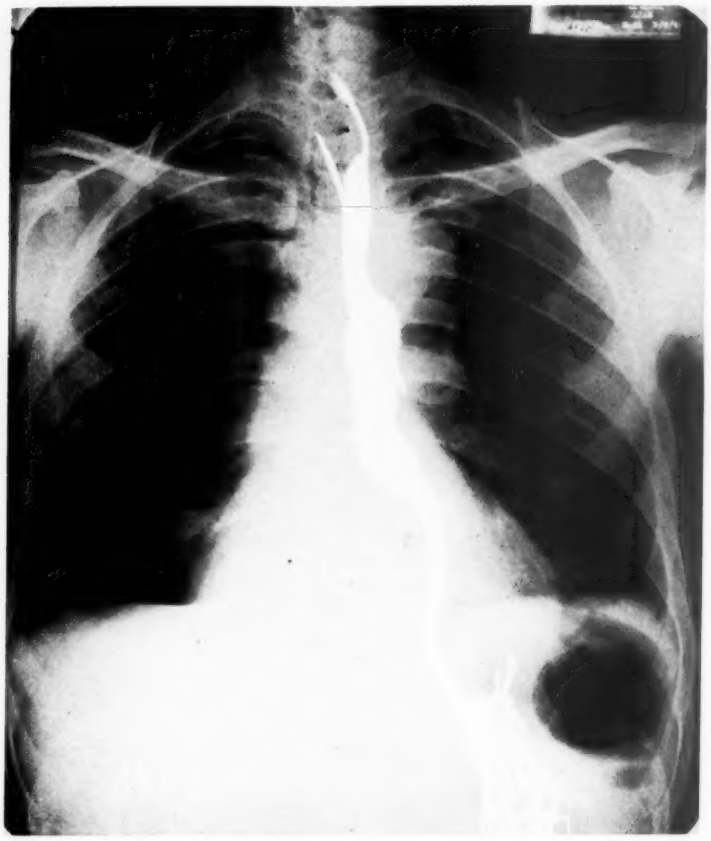

Fig. 2.—As seen in the anteroposterior view, the esophagus is displaced to the left and anteriorly. The shadow of the barium-filled esophagus has been retouched.

The esophagus showed interesting findings; it had an S-shaped course. At the top of the upper edge of the aneurysm the esophagus was displaced horizontally, and at the lower portion of the aneurysm the esophagus was pushed by it to the left. The stomach contained approximately 250 c.c. of clotted blood. There were scattered petechiae and mucosal hemorrhages throughout the intestines. The liver weighed 1,200 grams and was congested. Its margins were slightly rounded. The lobular markings were well defined. There were a few adhesions around the gall bladder. It contained normal, concentrated bile. The bile ducts were patent. The pancreas appeared rather large and firm but was otherwise normal.

The adrenals appeared normal. The brain was not removed.

Summary.—(1) Syphilitic aneurysm of the descending thoracic aorta; (2) rupture of the aneurysm into the left lung, emphysema; (3) distortion of the esophagus; and (4) benign nephrosclerosis, healed pyelonephritis, double right ureter.

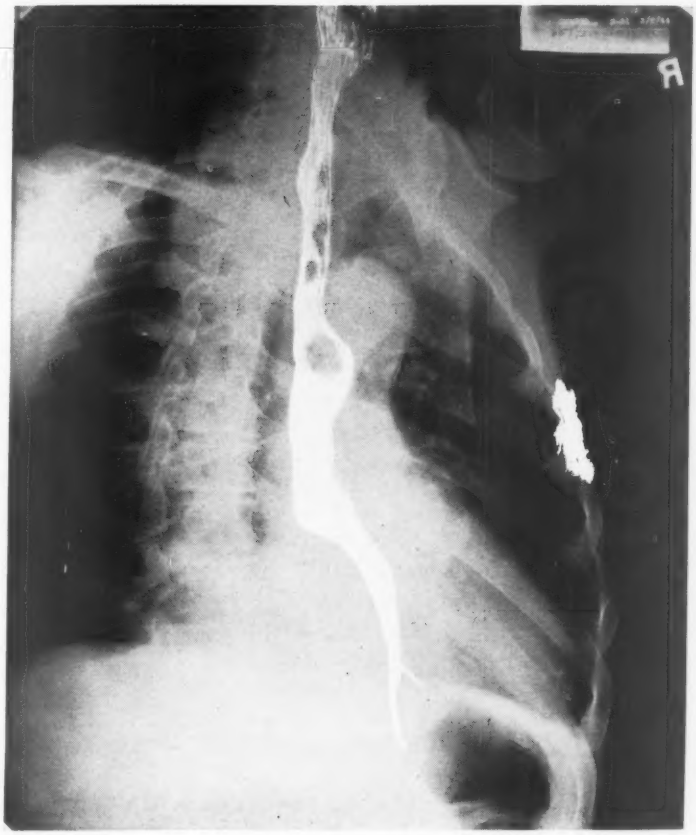

Fig. 3.—In the right oblique view, the anterior displacement of the esophagus is readily visible. The shadow of the barium-filled esophagus has been retouched.

DISCUSSION

The varied abdominal syndromes produced by thoracic disturbances as a whole, and by aortic aneurysms in particular, have been repeatedly reported. Coronary thrombosis, dissecting aneurysm, aortic lesions, pleurisy, pulmonary malignancy, and pneumonia have all masqueraded as primary gastrointestinal disease. Loewenberg and March[5] reported on a patient with aneurysm of the lower thoracic aorta in whom the sole symptom was peristent and intractable hiccup. Interestingly enough, this aneurysm also occurred at the hiatus of the diaphragm and was diagnosed premortem.

The anatomic relation of the esophagus to the aorta is of extreme importance in diagnosing the lesion. Roesler[6] and others have emphasized the value of determining the displacement of the barium-filled esophagus in cardiac roentgenology. Normally, the upper thoracic aorta occupies a position anterior and to the left of the esophagus. As the aorta and esophagus pass through the hiatus

of the diaphragm, the esophagus crosses over the aorta, at this point being anterior and somewhat to the left of the aorta. In the majority of aortic aneurysms, the aortic extension is posteriorly and to the left,[7] so that the esophagus is displaced posteriorly and to the right. The only aortic aneurysm that can displace the esophagus anteriorly and to the left is in an aorta at the hiatus. Roesler[6], Shanks, Kerley, and Twining,[8] and others[9-12] have stressed this anatomic relationship and have pointed out that this deviation of the esophagus may be produced by one other rare aortic abnormality; namely, right-sided aortic arch.

Another finding of note was the erosion of the ninth and tenth dorsal vertebrae. Many observers,[5, 6, 13] in commenting on aneurysms of the lower aorta, have emphasized the roentgen finding of destruction of the ninth, tenth, eleventh, and twelfth dorsal and the first lumbar vertebrae. In the majority of cases of aneurysm of the descending aorta, this is a nearly constant finding demonstrable by x-ray examination.

CONCLUSIONS

1. The relative incidence of aneurysms at various aortic sites is reviewed and a case of aneurysm of the descending thoracic aorta reported.
2. The clinical and roentgen features of this rare aneurysm are discussed.
3. Gastrointestinal syndromes produced by this lesion are mentioned and the relation of the esophagus to the aorta emphasized. Attention is also called to erosion of the vertebrae produced by aneurysm of the descending thoracic aorta.

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HEART BLOCK CAUSED BY FAT INFILTRATION OF THE INTERVENTRICULAR SEPTUM (COR ADIPOSUM)

DAVID M. SPAIN, M.D., and RICHARD T. CATHCART, M.D.
NEW YORK, N. Y.

The condition of "fatty heart," which has also been called at various times lipomatosis cordis, fatty infiltration of the myocardium, and cor adiposum, was a frequent clinical diagnosis over twenty-five years ago. In more recent years, this diagnosis has fallen into disrepute. Although it is true that "fatty heart" only rarely causes actual clinical manifestations of disturbed cardiac function, it is a definite entity that on occasion may not only be responsible for clinical evidence of heart disease, but may also be the sole important factor leading to the death of the individual.

Corrigan and Saphir* studied the anatomic changes in this condition. Their report consists of an analysis of fifty-eight necropsied cases that revealed anatomic evidence of fatty infiltration of the myocardium. Fat infiltration most likely originates from pre-existing, subepicardial fat. The usual site of infiltration is into the myocradium of the right ventricle. At times the myocardium may be completely replaced, or at least the few remaining fibers may be compressed as a result of the fat infiltration. The left ventricle is only occasionally involved and never to any significant degree. Isolated patches of fat are infrequently found beneath the endocardium of the left or right ventricle. At times fat may infiltrate down from the base of the heart into the interventricular septum. Because of the isolated patches occasionally found beneath the endocardium, it has been postulated that the fat originated not from direct infiltration, but as a result of transformation of pre-existing fibrocytes in situ into fat cells.

Corrigan and Saphir attributed the death of two of their patients solely to the fat infiltration. In twenty-nine of their patients important contributory symptoms were explained on this condition, while in the remaining twenty-three it was considered merely an incidental finding. It should be noted that fat infiltration is not to be confused with fatty degeneration that is secondary to infectious or anemic states.

The purpose of this report is to describe a case in which it is believed the manifestations of heart disease that consisted of right-sided heart failure and heart block were caused by fat infiltration of the right ventricular myocardium

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From the Laboratory of Pathology, Bellevue Hospital, and First Medical Division, Bellevue Hospital, (Columbia University, College of Physicians and Surgeons).

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*Corrigan, M., and Saphir, O.: Fatty Infiltration of the Myocardium, Arch. Int. Med. 52: 410, 1933.

and the interventricular septum. A careful search through the literature has failed to disclose any previously reported case of heart block caused by fat infiltration of the myocardium.

CASE REPORT

The patient, a 59-year-old white woman, housewife, was admitted to the First Medical Division of Bellevue Hospital, May 9, 1944, with the complaint of difficulty in breathing of five hours' duration. For nineteen years prior to admission she had noted transient swelling of the ankles. Recently this had been occurring at more frequent intervals and finally became constant. Twelve years prior to admission, she had a single attack of precordial, knifelike pain that continued for several hours. At that time her physician told her she had a heart attack and gave her digitalis for several weeks. She has never again had a similar attack. During the last five years, she has complained of frequent attacks during which "everything would go black, her heart would pound hard and fast," and there would be difficulty in breathing. These attacks were irregular, occurring either at rest or during activity, and lasted from several minutes to several hours. They seemed to be shortened following an injection by her physician; the nature of this injection could not be ascertained. For the past two years, the difficulty in breathing became constant and she was again given digitalis which she continued to take until this admission. The immediate episode that brought her to the hospital began while she was asleep. She was awakened by palpitation and dyspnea of an extremely severe character.

Physical examination on admission revealed an extremely obese, well-developed, 58-year-old white woman, slightly dyspneic and cyanotic. The head and neck were normal. The neck veins were not engorged. The lungs were normal. The left border of the heart was 15 cm. to the left of the mid-sternal line with the apex in the fifth intercostal space. The heart sounds were extremely distant with P_2 greater than A_2. There was a soft blowing systolic murmur heard best at the base. The rate was irregular and varied between 40 and 80; however, there was no pulse deficit. The abdomen was obese but otherwise not remarkable; no organs were felt. Slight pitting edema was present in both lower extremities. The remainder of the physical examination revealed nothing of significance.

The temperature on admission was 99.4° F., the pulse varied between 40 and 80, and the blood pressure was 108/68. The leucocyte count was 8,250, with 69 per cent polymorphonuclear leucocytes, 30 per cent lymphocytes, and 1 per cent eosinophilic leucocytes. Hemoglobin (Sahli) was 13 grams. Examination of the urine was normal. The erythrocyte sedimentation rate was 9 mm. in one hour. The Wassermann reaction was negative. The blood cholesterol was 286 mg. per cent. The basal metabolic rate was plus 6 per cent. The patient's weight was 187 pounds. Benous pressure measured 140 mm. of water. The circulation time, arm-to-tongue, was 22 seconds; arm to lung, 10 seconds. An electrocardiogram on admission showed marked left-axis deviation; auricular rate, 80; ventricular rate, 40; P-R_2, 0.22 second; QRS, 0.12 seconds; T_3 inverted (Fig. 1).

The patient responded moderately well to bed rest. The edema lessened with diuresis. The four-month stay in the hospital was characterized by many episodes that were apparently similar to the attacks she had had prior to admission. These attacks were of two types; each was accompanied by a moderate amount of cyanosis. During one, however, she would be markedly apprehensive and dyspneic without any change in physical signs. In particular, there would be no change in cardiac rate and no loss of consciousness. The second type would be more severe. During these attacks the patient would become comatose and the heart sounds would be almost impossible to hear. The heart rate on several occasions was markedly decreased. Asystole was never definitely noted, and there were never any convulsive seizures. Following these latter attacks, the patient would be entirely normal after a period of fifteen minutes and would lie quietly in bed for most of the day thereafter. The first type of attack was sometimes relieved by a sedative or a placebo. The second type was relieved by epinephrine. Repeated electrocardio-

grams revealed slightly variable but more or less constant heart block. The attacks first occurred about every ten days, but the interval between them tended to become shorter, and occasionally the attacks occurred several times in one day. Epinephrine relieved her for a time but later was of no value. Barium chloride had a similar effect. The patient was then given digitalis. Subjectively she felt better. During the first day of digitalization she had several mild attacks but thereafter was asymptomatic for two weeks. She then had a severe attack, following which the electrocardiogram revealed a complete heart block with a ventricular rate of 22 (Fig. 2). Thereafter she remained asymptomatic for one week, apparently none the worse for

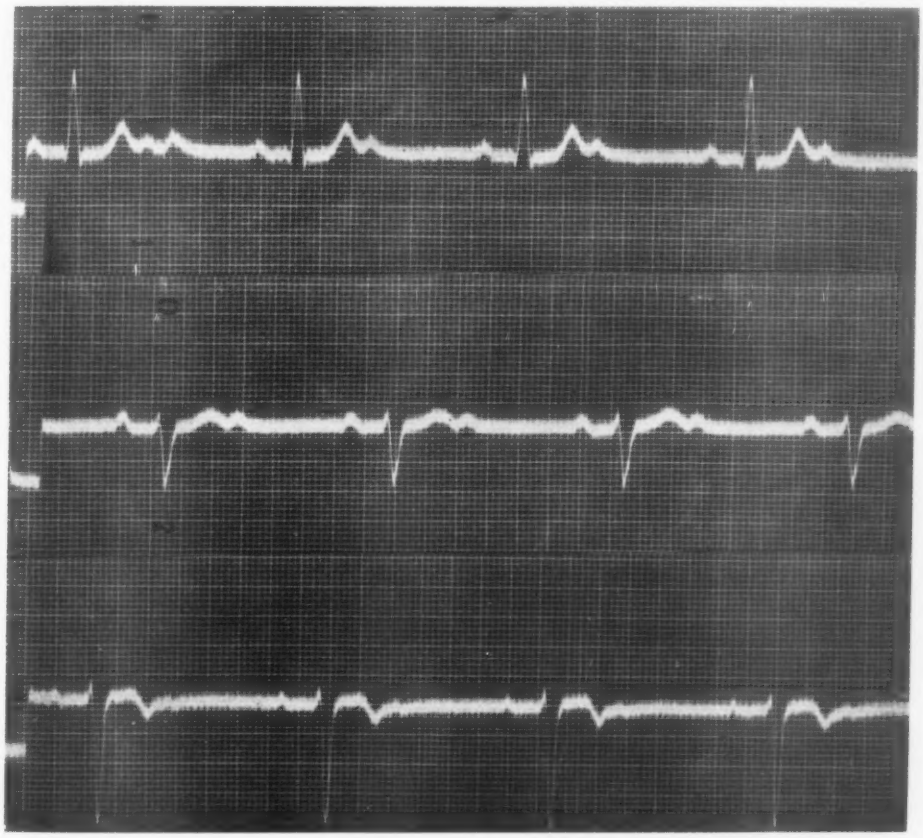

Fig. 1.—Electrocardiogram taken on admission revealing an auricular rate of 80 and a ventricular rate of 40.

the slow heart rate. Finally, on the one hundred tenth hospital day, she experienced another severe attack from which she did not recover despite the administration of epinephrine, coramine, and oxygen.

*Post-Mortem Examination** (Necropsy No. 32655).—The body was that of a well-nourished, extremely obese, elderly white woman, 5 feet, 3 inches in height, and weighing approximately 190 pounds. Marked dependent lividity was present and there was slight edema of the ankles.

*Description is limited to the pertinent findings.

The panniculus was everywhere quite thick and golden yellow in color. The heart weighed 570 grams. The epicardium was smooth and glistening, and there was a marked increase of subepicardial fat. Fat extended directly into the myocardium of the right ventricle and practically replaced all of the muscle fibers. This also was present to an insignificant degree in the left ventricle. Numerous sections through the interventricular septum, particularly in the region of the auriculoventricular node, revealed almost the entire myocardium to be replaced by fat. No similar change was present in the lower two-thirds of the interventricular septum. All of the chambers were dilated and the walls were flabby. The valve leaflets were all delicate and competent. The foramen ovale was not patent. The coronary ostia were widely patent and the coronary arteries were without evidence of atherosclerosis. The aorta was not dilated or tortuous and the wall was elastic. There were a moderate number of atheromatous plaques present.

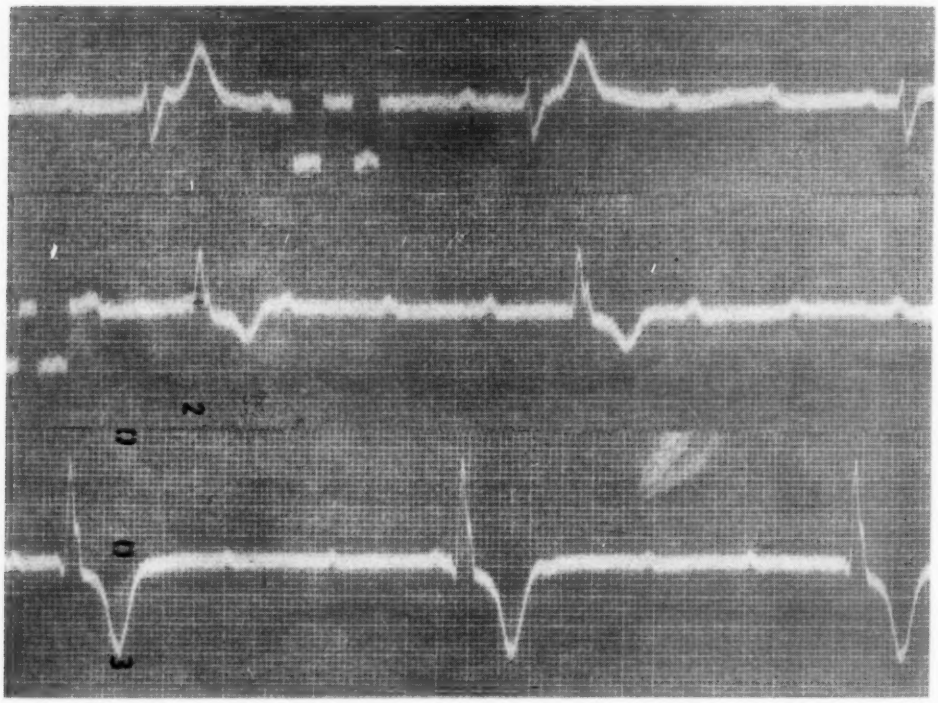

Fig. 2.—Electrocardiogram taken two weeks after digitalization revealing complete heart block with a ventricular rate of 22.

The lungs were congested. The liver weighed 2,000 grams and the lobular architecture was accentuated. The cut surface was deep red in color. The only other abnormal finding was the absence of both ovaries and Fallopian tubes (surgical).

Examination of histologic sections from the right ventricle and interventricular septum disclosed almost complete replacement of the myocardial fibers by fat cells (Fig. 3). Wherever myocardial fibers persisted, they were markedly compressed. The final anatomic diagnosis was obesity; fat infiltration of the myocardium, most marked in the right ventricle and interventricular septum; enlargement of the heart; atrophy of the myocardium; chronic passive congestion of th liver; congestion of the spleen; edema of the lungs; edema of the ankles; absence of both tube and ovaries.

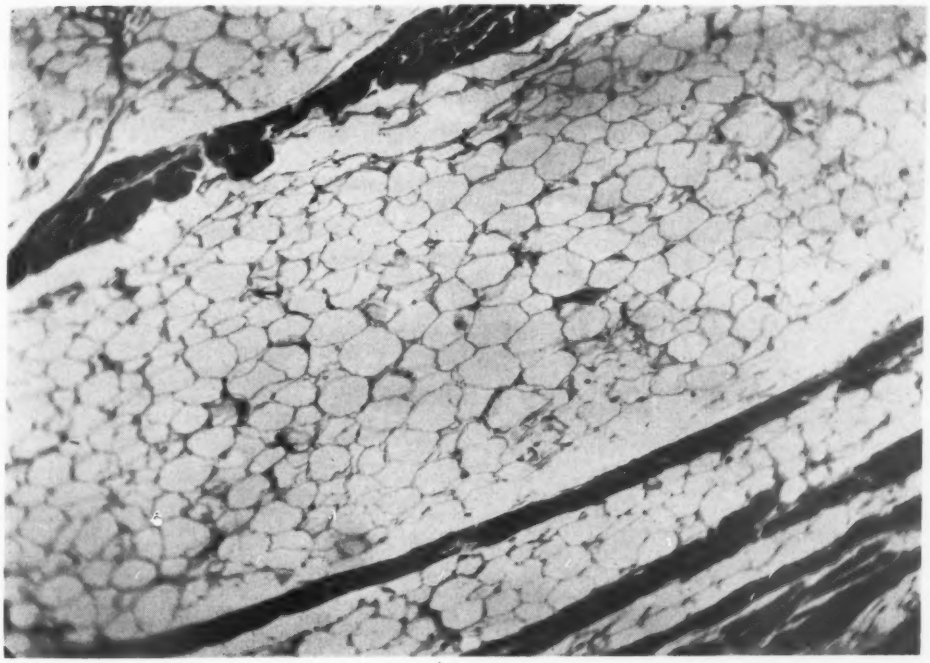

Fig. 3.—Photomicrograph of section taken through interventricular septum revealing extensive fat infiltration with compression of remaining myocardial fibers (hematoxylin and eosin, ×80).

DISCUSSION

Post-mortem examination of the heart revealed no evidence of rheumatic, syphilitic, hypertensive, or arteriosclerotic disease. In addition, there was no clinical evidence of avitaminosis or anemia, and the basal metabolic rate was plus 6. It, therefore, seems reasonable to assume that the clinical manifestations of heart failure that were present for many years can best be explained by the interference of the function of the right ventricle subsequent to the fat infiltration. Although heart block does occur without any demonstrable anatomic change in the heart, the extensive infiltration of the fat in the upper third of the interventricular septum undoubtedly played an important role in the development of the heart block in this patient.

Fat infiltration of the heart is most commonly associated with obesity, diabetes mellitus, and chronic alcoholism. In this particular case, the patient was very obese with extensive deposits of fat beneath the epicardium in the omentum and mesentery. This case differed somewhat in clinical course from that of the usual case of "fatty heart" in that the heart failure was chronic, and also in that heart block was present. On rare occasions the complete replacement of the myocardium of the right ventricle may so weaken the wall that rupture takes place.

SUMMARY

A case of extensive fat infiltration of the right ventricle and interventricular septum of the heart is presented.

The clinical manifestations of chronic right-sided heart failure and heart block is attributed to this anatomic change.

SYPHILITIC GUMMATOUS AORTITIS AS THE CAUSE OF CORONARY ARTERY OSTIAL STENOSIS AND MYOCARDIAL INFARCTION

Report of a Case

Tobias Weinberg, M.D., and Heinz F. Beissinger, M.D.
Baltimore, Md.

ALTHOUGH syphilitic aortitis per se is frequently observed at necropsy, the gummatous type of involvement is admittedly rare.[1,2] Furthermore, the association of coronary artery ostial stenosis and myocardial infarction is itself uncommon,[3] so that this association in a case of gummatous aortitis makes the following case even more unusual and prompts its report.

CASE REPORT

J. G., a white woman, aged 28 years, was admitted to The Sinai Hospital complaining of shortness of breath. Members of her family contributed the information that the patient had had a "cold" for several months and a cough for at least six months. According to the patient's story, she was well until four weeks before admission when she suddenly became extremely dyspneic after walking several blocks. The dyspnea was associated with aching pain in the right shoulder. From then on she had recurrent episodes of dyspnea upon exertion. About three days before admission she began to cough. Two days before admission her temperature became elevated and rose as high as 104° Fahrenheit. On occasion she had substernal pain which radiated to the right shoulder and to the right and left arms. The night before admission she expectorated blood. On the day of admission the sputum was observed to be brown. The positive findings were as follows:

Physical Examination.—The positive findings were as follows: Temperature, 102°; pulse, 140 per minute; and respirations, 32 per minute. The blood pressure was 90/74. She was obese. She was dyspneic and the mucous membranes were cyanotic. There was dullness to percussion posteriorly at the base of the right lung. Numerous râles were heard in the same area, as well as in the right upper and left lower lobes. The heart was found to be normal in size. The heart sounds were distant and the rhythm was regular. A systolic murmur was heard in the mitral area.

Laboratory Studies.—The red blood cells were 3.89 million per cubic millimeter; hemoglobin, 11.7 Gm.; and white blood cells, 23,800, of which 82 per cent were of the neutrophilic series. The blood urea nitrogen was 80 mg. per cent. The carbon dioxide combining power of the blood was 78.2 volumes per cent. Examination of the sputum failed to reveal the presence of any pneumococci. Blood for a Wassermann test was not obtained.

Course in Hospital.—The condition of the patient became rapidly worse. The blood pressure and pulse became unobtainable. Digitalis therapy was instituted, followed by sulfathiazole and adrenal cortical extract. Therapy, however, was ineffectual and the patient died less than twenty-four hours after admission. The clinical impression was bronchopneumonia. The terminal temperature was 106° Fahrenheit.

From the Laboratories of The Sinai Hospital, Baltimore, Md.
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Necropsy Findings.—The autopsy was performed almost four hours after death. The contributory findings were as follows: The heart was not enlarged and weighed 250 grams. Both ventricles were moderately dilated. The myocardium of the left ventricle was yellowish-brown with distinctly yellowish areas visible in the papillary muscles. The valve leaflets and cusps were not remarkable. Arising within the sinuses of Valsalva, corresponding to the right and left aortic cusps, there was a broad plaquelike area of thickening upon the intimal surface of the aorta which measured approximately 3 by 2 centimeters. It completely encircled and narrowed the orifice of the left main coronary artery and also encroached upon the orifice of the right main coronary artery but did not encircle it (Fig. 1). Beyond their orifices the coronary arteries were

Fig. 1.—Heart opened to show aortic valve and encroachment upon coronary artery ostia by plaque at base of aorta.

widely patent and thin-walled. The aorta contained two more plaquelike areas of somewhat smaller size in the ascending and tranverse arches of the aorta. The remainder of the aorta was elastic and contained only scattered atherosclerotic streaks. There was about 200 c.c. of clear, straw-colored fluid in the right pleural cavity and 300 c.c. of a similar fluid in the left pleural cavity. The sectioned surfaces of the lungs showed extensive edema.

Fig. 2. Fig. 3.

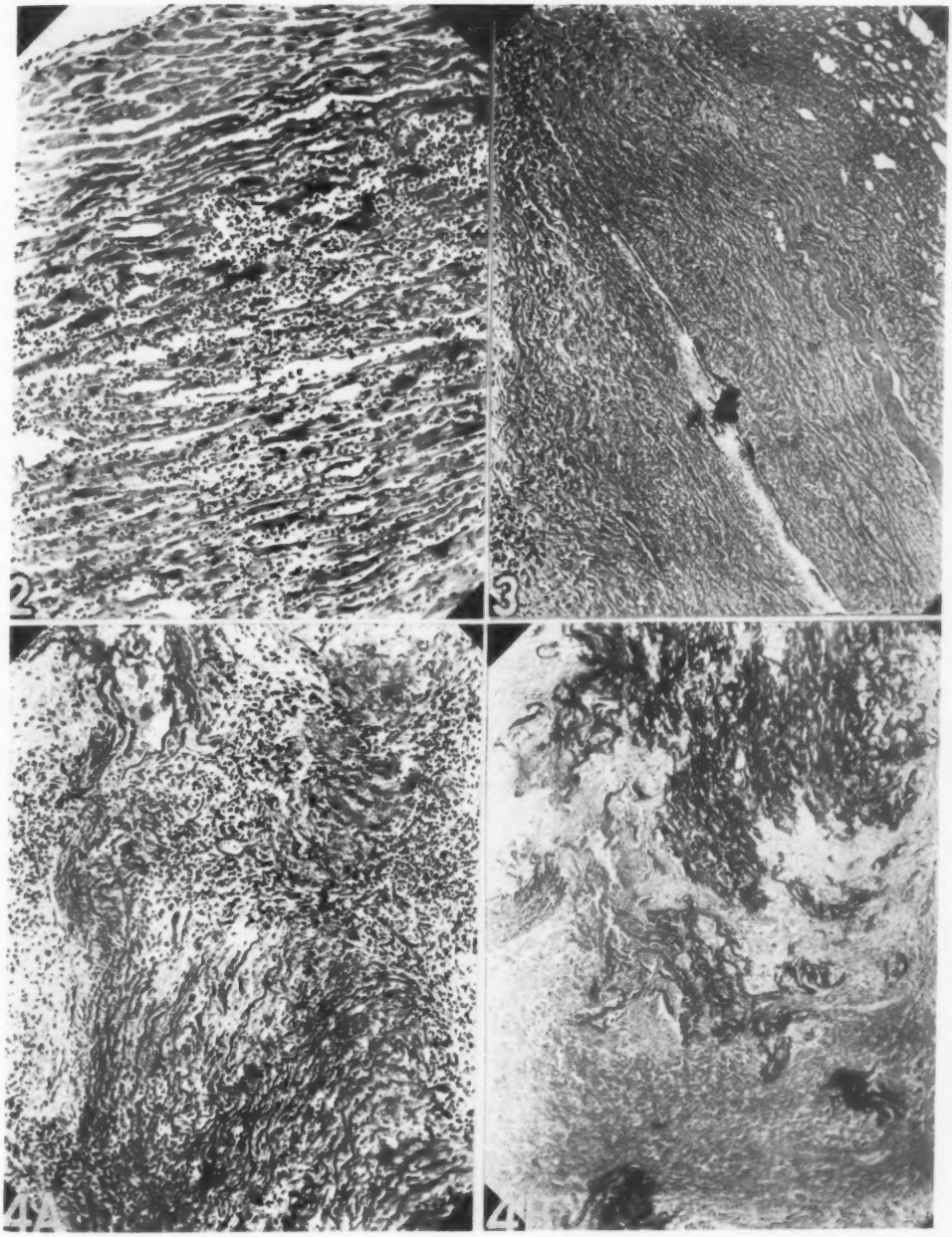

Fig. 4.

Fig. 2.—Section of myocardium of left ventricle showing infarction.

Fig. 3.—Section through plaque at base of aorta showing gummatous alteration.

Fig. 4.—*A*, Section of aortic plaque showing areas of medial destruction with fibrous replacement and plasma cell and lymphocytic infiltration. *B*, Weigert's elastica-van Gieson stain of portion of plaque in aorta showing marked destruction of the elastic tissue in the media.

Microscopic Findings.—The sections of the myocardium taken from the posterior wall as well as from the papillary muscles of the left ventricle showed tinctorial changes, loss of cross-striations, and areas of extensive necrosis with dense polymorphonuclear infiltration (Fig. 2). The sections of the large plaques observed in the aorta showed a marked intimal thickening, consisting partly of cellular and partly of collagenous connective tissue within which there were large areas of necrosis as well as fibrinoid degeneration. The areas of necrosis assumed a granular amorphous basophilic character and, in some instances, were in proximity to large collections of plasma cells and lymphocytes (Fig. 3). In some areas the media was practically completely destroyed with resulting fibrous replacement and plasma cell infiltration (Fig. 4). Many blood vessels in the media and adventitia were surrounded by collections of plasma cells and lymphocytes, and some showed a cellular intimal proliferation. The adventitia in these areas was thickened. Stains for spirochetes performed by both the Levaditi and Dieterle techniques failed to reveal their presence. Sections of the other organs merely confirmed the gross observations.

COMMENT

According to Held and Goldbloom[1] and Gordon, Parker, and Weiss,[2] only a few cases of gummatous aortitis have been reported in the recent literature. The first-mentioned authors claim to have found only three instances in their review of the literature. Gordon and co-authors, in a review of their own cases, found eight instances of gummatous alteration in a series of 360 cases of syphilitic aortitis.

Both Burch and Winsor[3] and Love and Warner[4] have made extensive analyses of the association of coronary ostial stenosis due to syphilitic aortitis and acute myocardial infarction. The former[3] found three of a series of 185 myocardial infarctions to be due to syphilitic coronary artery ostial stenosis, and accordingly concluded that myocardial infarction as a result of syphilis is rare. In a series of 193 cases of syphilitic aortitis they found forty in which there was narrowing of the ostia of one or both coronary arteries. Of these, only three had myocardial infarction. Love and Warner[4] analyzed their series of fifteen cases in which there was stenosis of either one or both coronary ostia. In eight of the fifteen cases there was marked fibrosis of the myocardium. In four cases there was acute myocardial infarction as evidenced by leucocytic infiltration. Corrigan,[5] in his discussion of myocardial infarcts and syphilitic aortitis, stated that morphologic evidence was rarely demonstrated at the post-mortem examination. Von Glahn[9] collected 687 cases of syphilitic aortitis and found among them 120 instances of occlusion or stenosis of one or both coronary artery orifices and only four infarcts of the myocardium.

Most authors emphasize the relatively early age at which syphilitic coronary artery stenosis is found. Bruenn[6] gives the average age as 34 years. Burch and Winsor[3] place the average age at 40 years. The youngest case they found was in a person 20 years of age. Gordon, Parker, and Weiss'[2] youngest patient with gummatous aortitis was 32 years old. Clawson[8] reported only one case occurring in the third decade. Other authors[5,7] report cases in patients in their thirties but none younger.

From the foregoing brief review of some of the pertinent literature on the subject, it is obvious that the present case is an instance of syphilitic aortitis

associated with coronary ostial stenosis in an individual manifesting the effects of the disease at an even earlier age than that most commonly recorded in the literature. The findings of acute myocardial infarction in our case places it in another group of relatively rare observations. The same is also true of the finding of gummatous aortitis.

The microscopic findings in our case are so characteristic that in spite of the lack of corroborative evidence in the form of a positive serologic test for syphilis or the finding of spirochetes, we feel quite certain of the etiologic character of the aortic lesion described.

SUMMARY

A case of syphilitic gummatous aortitis is reported occurring in a 28-year-old woman and associated with coronary artery ostial stenosis and acute myocardial infarction.

Attention is called to the rarity of each of the findings individually and as a group, particularly in an individual in the third decade of life.

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Abstracts and Reviews

Selected Abstracts

Lindquist, T.: Intermittent Claudication and Vascular Spasm: I. Is Vascular Spasm a Contributory Cause of Intermittent Claudication in Patients With Structural Disease of the Arteries? Acta med. Scandinav. **121**:32 (I), 1945.

The author investigated the mechanism of the cutaneous pallor and coolness observed during attacks of intermittent claudication in an attempt to determine whether this represented a true vasospasm with reduction in muscle blood supply or whether it was simply the excessive effect on organically narrowed vessels of the slight cutaneous vasoconstriction that has been described in normal persons in association with exercise.

Oscillometric records were made on eight patients with intermittent claudication. The cuff was applied to the thigh or upper calf rather than the ankle since it was felt that most of the muscular branches of arteries were given off above the latter point and that measurements at the ankle might reflect changes in vessels supplying mainly skin or supporting structures. A special apparatus was used to record the relatively small pulsations of the thigh and calf.

It was found that the amplitude of pulsations decreased markedly in some patients when cramps appeared but in others the amplitude increased in a fashion similar to the normal response. The occurrence of these two types of reaction appeared to be independent of the integrity of the sympathetic supply to the limb, for both occurred in patients with and without previous lumbar sympathectomy or block.

The possibility that the diminished oscillations were due to less blood reaching the more distal muscles because it was being "stolen" by more proximal muscles was considered and rejected. It was concluded that true vasospasm did occur in some patients with intermittent claudication but not in all and that it was independent of the sympathetic innervation of the affected limb.

SAŸEN.

Griffith, G. C., and Bailey, E. T.: The Treatment of Rheumatic Fever by Roentgen Ray Irradiation. Ann. Int. Med. **24**:1039 (June), 1946.

This report concerns experiences gained from irradiation therapy among 201 patients in the rheumatic fever unit at the U. S. Naval Hospital, Corona, California. All the patients had been ill with rheumatic fever which had been present for six months or more. The patients were divided into three groups. Those in the first group received 100 roentgens through the myocardium at weekly intervals for five successive weeks. Those in the second received 100 roentgens through the myocardium and over the middle and lower cervical sympathetic ganglia every week for five successive weeks. The patients in the third group received no treatment but went through the same mechanical routine as did those in Groups I and II (a lead filter was used to block out the roentgen rays). The results of this program were carefully analyzed. It was concluded that there was no greater improvement in the patients treated than in those who did not receive irradiation therapy. There was no demonstrable therapeutic value from roentgen ray therapy in the primary or in the recurrent attacks of rheumatic fever. The final conclusion is that roentgen ray therapy is not a useful procedure in the treatment of rheumatic fever. WENDKOS.

Jones, M., and Scarisbrick, R.: The Effect of Exercise on Soldiers With Neurocirculatory Asthenia. Psychosom. Med. **8**:188 (May-June), 1946.

The influence of effort syndrome on the reaction to exercise was studied at the Mill Hill Hospital, London, England. Effort syndrome was classified into three groups: (1) where poor physical endowment is the primary factor in producing symptoms; (2) where poor physical endowment is the primary factor in producing symptoms but the patient responds in a neurotic manner to his constitutional inferiority; (3) primarily neurotic. Since the hospital is a neurosis center, patients belonging to Group 1 were rarely seen.

Comparisons were made of the effects of exercise on thirty-five normal control subjects, twenty-five patients with effort syndrome in Group 2, and ten patients with effort syndrome in Group 3. The subjects undertook two tests: standard work, in which they pedaled a bicycle ergometer for five minutes, and maximal work, in which they pedaled to the point of exhaustion in ten minutes. Observations were made on the pulse rate and blood lactate level.

The patients with effort syndrome in Group 2 (constitutional) showed a mean blood lactate rise of 28.9 mg. per cent after standard exercise. The corresponding figure for the normal controls was 21.1 mg. per cent. The patients in Group 3 (psychogenically produced effort syndrome) showed a blood lactate rise similar to that of those in the control group. The pulse rate response to standard work was a greater rise and a slower decrement in those in the effort syndrome group than in those in the control group. Group 2 patients had a higher rise and a slower decrement than did the Group 3 patients.

After maximal work, the mean blood lactate rise for the control group was 78.0 mg. per cent and for the patients with effort syndrome, 50.2 mg. per cent. The mean lactate rise was essentially similar for the patients with effort syndrome in both Groups 2 and 3. The pulse rate response to maximal work, in contrast to the effect of standard work, was similar in both patients and normal controls.

It appeared from these observations that a satisfactory differentiation between Group 2 (constitutional) and Group 3 (psychogenically produced) effort syndrome can be made on the basis of the blood lactate response to standard exercise. When maximal exercise is used, it is evident that patients with effort syndrome, unlike the normal controls, give up exhausting physical work before a "physiological" end point is reached, due to what amounts to effort phobia.

LAPLACE.

Westermark, N.: A Method for Determining the Blood Pressure in the Pulmonary Artery. Acta. Radiol. **26**:302 (No. 3), 1946.

By making multiple roentgenograms of the chest in subjects performing a modified Valsalva experiment by blowing into a closed system in which pressure was measured, a point was found at which a marked diminution in the diameter of the pulmonary vascular shadows appeared. In twenty normal subjects this phenomenon occurred at a pressure of 25 to 30 mm. of mercury. This was believed to approximate closely the systolic pressure in the pulmonary arterial system. Ninety patients with mitral stenosis were studied in a similar manner. Twenty-two of these had clinical signs of a mild valvular lesion and showed pressures within the normal range. In thirty patients with moderate mitral stenosis the pressures ranged from 30 to 60 mm. of mercury, while thirty-eight with severe mitral stenosis required a pressure of over 60 mm. of mercury to produce significant decreases in the size of their pulmonary vascular shadows. It is believed that this method is a satisfactory nonsurgical procedure for determining pulmonary blood pressures in man.

SAŸEN.

Pereira, A. de Sousa.: The Innervation of the Veins: Its Role in Pain, Venospasm and Collateral Circulation. Surgery **19**:731 (May), 1946.

The nerve supply to the veins contains afferent sensory pathways in addition to the efferent vasomotor components. Mechanical or chemical stimulation of the veins causes pain. The relief of venous pain and venospasm in acute phlebitis and thrombophlebitis by the injection of 1

per cent novocain into the affected vein, or by the anesthetic block of the sympathetic chain, lasts for a longer period than the anesthetic action of the drug can account for. This suggests that venospasm may play an important role in the mechanism of pain. Venography in the author's cases demonstrated that venospasm extended far beyond the phlebitic or thrombosed vein. This venospasm may be relieved by peripheral anesthesia of the venous wall or by interruption of the efferent pathways of the sympathetic chain.

In cases of thrombophlebitis it was observed that repeated anesthetic blocks of the sympathetic chain with procaine hydrochloride, perivenous sympathectomy, or resection of the regional sympathetic chain was followed by an increase in collateral venous circulation. These investigations have demonstrated that physiologic or anatomic interruption of the innervation of the veins may relieve the pain and the venospasm and also increases the development of collateral circulation. The facts observed suggest that the plan of the innervation of the veins in relation to pain, spasm, and collateral circulation is similar to that of the afferent sensory and the efferent vasomotor pathways of the arteries. NAIDE.

Guthrie, D., and Gagnon, G.: The Prevention and Treatment of Post-Operative Lymphedema of the Arm. Ann. Surg. **123**:925 (May), 1946.

The most important factor in prevention of lymphedema of the arm following radical mastectomy is the avoidance of infection. Prolonged immobilization of the arm following the operation should be condemned. Absolute free and early mobilization should be instituted. It is as important to mobilize the arm following radical mastectomy to prevent edema as it is to exercise the legs for prevention of phlebothrombosis and thrombophlebitis following operation in the pelvis. The patient is requested to move her arm as soon as she reacts from the anesthesia. If roentgenotherapy is indicated, one should avoid a destructive type of dermatitis.

The authors recommend treatment of post-operative lymphedema by the Beck operation. Five strips of celloidin are inserted into the subcutaneous tissue and left in place for three weeks. This procedure aids in the development of collateral channels The Kondoleon operation has proved to be of no value. NAIDE.

Stead, E. A., Jr., Brannon, E. S., and Brannon, A. J.: Concentrated Human Albumin in the Treatment of Shock. Arch. Int. Med. **77**:564 (May), 1946.

Tests of the usefulness of human albumin as substitutes for plasma have been made by observing the effects of giving it intravenously to seven normal subjects and thirty-four patients with circulatory failure. The following studies were made on these subjects: mean atrial pressure, oxygen consumption, optical recording of arterial pressure, oxygen content of arterial and right atrial blood, cardiac output, plasma volume, and hematocrit.

No untoward effects were noted. None of the patients experienced chills, fever, urticaria, pulmonary edema, or circulatory collapse.

Seven normal subjects received 1 liter of a 5 per cent solution of human albumin intravenously within a period of fifteen to thirty-one minutes. Two consistent changes were noted. The atrial pressure always rose and the hematocrit reading and concentration of hemoglobin always fell. The arterial pressure, cardiac rate, consumption of oxygen, and arteriovenous oxygen difference showed no consistent change.

Studies were also made on thirteen patients with circulatory insufficiency following acute hemorrhage, on seven additional patients following injuries to the chest, and on two patients with hemopericardium resulting from penetrating wounds. All but two of these patients received 50 Gm. of a 25 per cent solution of human albumin. The results of therapy in patients with hemorrhage were uniformly good. The results of therapy in the patients with burns, dehydration, and infection were satisfactory.

The average increase of plasma volume produced by 1 Gm. of albumin was 14 cc. Although albumin is not as useful in the treatment of shock as is whole blood, albumin is nevertheless an extremely useful substitute for plasma. From the standpoint of speed and convenience of ad-

ministration, convenient packaging, small bulk, stability under varying temperatures, and absence of bacterial contamination, concentrated albumin is ideal. In civilian practice where whole blood and plasma are readily available, albumin may not be used extensively in the treatment of shock. Under the conditions of war, concentrated albumin has many advantages.

BELLET.

Flett, D. M., and Powell, W. N.: Acute Bacterial Endarteritis. J.A.M.A. **131**:397 (June 1), 1946.

These authors present what they consider to be the first report of endarteritis of the ductus due to Diplococcus pneumonia. This infection was arrested on the thirteenth day after a total of 3,875,000 units of penicillin had been given within a period of twenty-eight days. At a later date, the patent ductus was ligated. Six months after the original observation the patient had gained 25 pounds in weight and the auscultatory phenomena previously observed were no longer present. The patient was apparently well ten months after the original period of treatment.

BELLET.

Segers, M.: A Study of the Gaskell Effect. Arch. internat. de pharmacodyn. et de thérap. **71**:173 (Nov.), 1945.

One of the most typical actions of the vagus nerve on the heart is that of producing positive variations of polarization, known as the Gaskell effect. In order to determine the factors involved in this phenomenon, a study was made of the action of acetylcholine on the electrical charges on the surface of the myocardium of the frog: in the rhythmically beating heart the positive potentials are due to the disappearance of late negative potentials; in the nonbeating heart, acetylcholine does not produce any positive variation. The Gaskell effect results, therefore, not from a modification of the current of demarcation of the myocardium, but from a modification of the evanescent state of polarization represented by the after-potentials. The action of adrenalin is identical but is opposite in direction.

The Gaskel effect is often regarded as the factor responsible for the inhibitory action of the vagus. This view is acceptable but it must be understood that the mechanism is not the only one involved since the cardio-moderator effects of the vagus can occur in the absence of any variation of polarization.

The late negativity of the heart is accompanied by a postsystolic contracture occupying the interval which separates the beats. Under the influence of acetylcholine, the postsystolic contracture disappears at the same time as the late negativity. Acetylcholine does not, however, produce any change in tonus in the resting heart.

The after-potentials demonstrate the existence of a state of supernormality produced by the heart beats and suppressed by acetylcholine. The Gaskell effect corresponds, therefore, to suppression of a state of excitation and not to a true inhibition of the heart.

LAPLACE.

Wallace, L., Katz, L. N., Langendorf, R., and Buxbaum, H.: Electrocardiogram in Toxemias of Pregnancy. Arch. Int. Med. **77**:405 (April), 1946.

The authors discuss the presence of electrocardiographic changes during toxemias of pregnancy. Their series included twelve cases of toxemia of pregnancy without eclampsia. Group I consisted of two patients who developed acute left ventricular failure at the time of labor. Group II was made up of four patients who manifested no heart failure but presented electrocardiographic changes. Group III consisted of six patients in whom there was no evidence of heart failure and in whom no electrocardiographic abnormalities were observed despite the presence of toxemia.

In Group I, electrocardiographic changes were observed which were characterized by inverted T waves in Leads I, CF_2, and CF_4 and by the absence of any pronounced S-T deviation or changes in the QRS complex. In one of the patients, complete restitution to normal occurred within

fifteen weeks; the other could not be followed. The authors suggest that the changes observed in patients with toxemia who experienced cardiac failure simulate rather closely the changes occasionally seen in acute nephritis.

In Group II, during the last trimester of pregnancy, inversion of the T wave in CF_2 and CF_4 was present; this reverted to normal within one week following delivery. Similar findings were occasionally observed in normal persons as well as in patients with toxemia of pregnancy.

The possible causes of these electrocardiographic abnormalities are discussed.

BELLET.

Merrill, A. J.: Edema and Decreased Renal Blood Flow in Patients With Chronic Congestive Heart Failure: Evidence of "Forward Failure" as the Primary Cause of Edema. J. Clin. Investigation **25**:389 (May), 1946.

In patients with chronic congestive heart failure the cardiac index (liters per square meter per minute) tends to be lower than average normal. These patients also exhibit a reduction in renal plasma flow, glomerular filtration rate, and sodium clearance.

Renal venous congestion is not responsible for the reduced renal plasma flow because no correlation is found to exist between the level of venous pressure and the volume flow of blood through the kidneys. On the other hand, a significant correlation is found between renal plasma flow and the cardiac index; that is, when cardiac output is reduced, renal plasma flow is reduced (frequently to a greater extent than the cardiac output). Associated with the reduction in renal plasma flow is a significant decrease in sodium clearance which is accounted for chiefly by a low filtration rate rather than by increased tubular reabsorption of sodium. Sodium retention then leads to edema formation.

The data indicate that "forward" rather "backward" failure is the cause of edema formation in chronic congestive heart failure despite the fact that many patients have cardiac indexes which fall well within the normal range. This apparent discrepancy is explained by suggesting that no absolute level of cardiac output exists below which patients develop cardiac failure: the patient with thyrotoxicosis may have a normal or increased cardiac index and still develop congestive heart failure if the cardiac index fails to meet metabolic demands.

FRIEDLAND.

Zeek, P. M.: Heart Weight: II. The Effect of Tuberculosis on Heart Weight. Arch. Path. **41**:526 (May), 1946.

The author points out that emaciation in tuberculous patients and not tuberculosis per se is the important factor for the common finding of a small heart. In the presence of a well-maintained nutrition, a tuberculous patient should have a heart of normal weight.

GOULEY.

Postoloff, A. V., and Cannon, W.: Genesis of Aortic Perforation Secondary to Carcinoma of the Esophagus. Arch. Path. **41**:533 (May), 1946.

To the total series of sixty cases reported to date, the authors add two of their own cases of perforation of the aorta by carcinoma of the esophagus. In both of these women, aged 76 and 38 years, respectively, there was a history of progressive dysphagia and sudden death preceded by hemorrhage from the nose and mouth.

Necropsy revealed that the wall of the aorta had become undermined, leading to small intimal perforations, not because of actual tumor cell invasion of the media and intima, but as a result of cellular infiltration of the vaso vasorum with secondary thrombosis and fibroblastic reaction in those vessels.

GOULEY

Wexler, J., Whittenberger, J. L., and Himmelfarb, S.: An Objective Method for Determining Circulation Time From Pulmonary to Systemic Capillaries by the Use of the Oximeter. J. Clin. Investigation **25**:447 (May), 1946.

The oximeter is an instrument which measures continuously the oxygen saturation of arterial blood by means of photoelectric colorimetry of the intact fully flushed ear. The interval between the beginning of a deep breath of 100 per cent nitrogen and the beginning of the downward deflection of the recording device (a galvanometer) was considered to be the time required for the unsaturated blood to pass from the lungs to the ear. In thirty-five subjects without heart disease the range of values was 4.1 to 7.0 seconds with an average value of 5.2 seconds. Twenty-three subjects (66 per cent) were within the range of 4.6 to 5.5 seconds and the variation on repeated tests in any individual did not exceed 1.8 seconds. Of course the recorded values are probably higher than the true pulmonary to systemic capillary circulation time since the measurement includes the time of inspiration, diffusion time of the nitrogen in the residual air, the galvanometer lag, and the reaction time of the observer. The method promises to be useful and accurate in that it is objective, requires a minimum of cooperation on the part of the patient, and eliminates the variable arm-to-lung segment in the usual method of measuring the circulation time.

FRIEDLAND.

Heymans, C., and Capet, L.: The Influence of Magnesium and Calcium on the Proprioceptive Regulation of Arterial Pressure. Arch. internat. de pharmacodyn. et de thérap. **51**:164 (Nov.), 1945.

It is well known that magnesium has a depressant action on the central nervous system which can be neutralized by calcium. On the other hand, calcium deficiency has been shown to cause a diminution of the aortic and carotid sinus reflexes which control the proprioceptive regulation of arterial pressure. An investigation was therefore made of the reciprocal influences of magnesium and calcium on the vasomotor reflexes originating in the carotid sinus and of the action of calcium on arterial hypertension produced by suppression of the four aortic and carotid sinus nerves. The studies were performed on dogs and led to the following conclusions:

1. Magnesium sulphate can depress and almost paralyze the vasomotor reflexes concerned in the proprioceptive regulation of general arterial pressure.

2. Calcium chloride or thiosulphate can re-establish the vasomotor reflexes of the carotid sinus which have been depressed or paralyzed by magnesium.

3. Suppression of the four depressor nerves produces a substantial hypertension which may be permanent or transient. The fall of arterial pressure after hypertension is produced by suppression of the depressor nerves is due to cardiovascular collapse caused by the hypertension.

4. Calcium administered intravenously protects the heart against the effects of sudden hypertension produced by suppression of the four depressor nerves.

5. Calcium administered intravenously, on the one hand, stimulates the heart but, on the other hand, increases and maintains the hypertension produced by suppression of the depressor nerves.

LAPLACE.

Book Reviews

PHONOCARDIOGRAPHIE, AUSCULTATION COLLECTIVE (ACOUSTIQUE—TECHNIQUE—CLINIQUE). By C. Lian, G. Minot, and J. J. Welti. Paris, 1941, Masson & Cie, 253 pages.

This monograph on phonocardiography represents years of work on this subject by the authors. It is complete in scope and quite extensive in detail. In the first place, there is a discussion of principles of physics involved in the recording and interpretation of heart sounds; this is followed by a detailed description of the various apparatus used in making their studies of heart sounds, venous pulse, and apex impulse. They have been able to record simultaneously the electrocardiogram, the phonocardiogram, the venous pulse tracing, and the electrokymogram or tracing of the apex impulse. Further, in the mechanical domain, they have developed a good method for recording heart sounds on phonograph records and for their rendition over a loud speaker for the benefit of group auscultation. In addition to the studies on cardiology, they present a chapter on recording of vascular murmurs and another chapter on the recording of sound tracings of respiration and of abdominal ascitic waves produced by percussion.

For students of cardiology this monograph will serve as a work of reference and as an important painstaking contribution to the special literature of the subject of phonocardiography. The chapters on doubling of the first and second sounds, on the third sound, and on gallops are well written and well illustrated with many figures.

WILLIAM C. KUZELL, M.D.

THE VENOUS PULSE AND ITS GRAPHIC RECORDING. By Franz M. Groedel, M.D. New York, N. Y., 1946, Brooklyn Medical Press, Inc., 223 pages.

This book describes the author's experience in recording the venous pulse and his views on interpretation of the usual waves as well as a number of additional waves which appear in his records. There is also a section on the pneumo-cardiogram and the esophagocardiogram. The illustrations are good.

J. K. LEWIS, M.D.

ELECTROCARDIOGRAPHY IN PRACTICE. By Ashton Graybiel, M.D., and Paul D. White, M.D., with the assistance of Louise Wheeler, A.M., and Conger Williams, M.D. Second edition. Philadelphia and London, 1946, W. B. Saunders Company, 458 pages, 323 illustrations. Price $7.00.

This useful book has been expanded and much new material has been added. The original format and plan have been retained with the presentation of the clinical information and electrocardiographic interpretations on one page and the electrocardiograms shown on the facing page. Over fifty figures have been added to this new edition and more attention is directed to the precordial electrocardiogram. Some consideration is given also to the more fundamental aspects of electrocardiography. New charts have been included which summarize in tabular form the characteristics of the various arrhythmias, the electrocardiographic findings in various types of heart disease and conditions secondarily affecting the heart, and the electrocardiographic effects of many drugs and physiological processes. The valuable and instructive section of the book containing "test electrocardiograms" is made up entirely of new material.

As in the first edition of the work, "coronary heart disease" is given as an etiological diagnosis for many of the electrocardiographic deviations discussed. Although it is agreed that coronary arterial disease is accountable for the majority of these abnormalities, this usage may incline some readers to the usually unjustified practice of making pathological diagnoses such as this from electrocardiographic data alone in the absence of such extensive clinical information as is available with these cases. Doctors Graybiel and White state that they have found a lead from the right sternal margin (precordial position 1) rarely useful. This experience is not in accord with that of other observers who have been interested in multiple precordial leads and may account for the lack of emphasis in this volume upon the contrast in form of the precordial electrocardiogram in right and left ventricular hypertrophy. The atlas system of presentation makes for some repetition of discussion. While this may serve a useful teaching purpose, it may be disadvantageous when unintended inconsistencies occur. For example, in an early section of the book, it is said that the records under consideration display both complete atrioventricular block and bundle branch block, whereas at a later point, the writers amplify the discussion to indicate correctly that these diagnoses cannot be made together because of uncertainty regarding the site of the idioventricular pacemaker. The illustrations are very clear and well presented, although Fig. 80, page 119, is inverted and reversed. The typography and paper are of good quality.

This book should serve well as an aid in the interpretation of electrocardiograms as they are met in general practice, the purpose for which it was written. It should be particularly valuable in that it provides a larger number of quite typical electrocardiograms for study and review.

FRANCIS F. ROSENBAUM.

American Heart Association, Inc.

1790 Broadway at 58th Street, New York, N. Y.

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty-three eminent physicians who represent every portion of the country.

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